Obesity in Dogs and Cats: A Metabolic and Endocrine Disorder

Debra L. Zoran, DVM, PhD

Obesity is defined as an accumulation of excessive amounts of adipose tissue in the body, and has been called the most common nutritional disease of dogs in Western countries.1–5 There have been a variety of surveys reporting the incidence of obesity in various parts of the world, and in these studies the incidence of obesity ranges from 22% to 44% depending on location and criteria.5–9 However, in the past 10 years, most investigators have agreed that at least 33% of the dogs presented to veterinary clinics are obese, and that the incidence is increasing as human obesity increases in the overall population.1 This statistic is important because obesity is not just the accumulation of large amounts of adipose tissue, but is associated with important metabolic and hormonal changes in the body. These metabolic and hormonal changes are the focus of this review, and are associated with a variety of conditions, including osteoarthritis, respiratory distress, glucose intolerance and diabetes mellitus, hypertension, dystocia, decreased heat tolerance, some forms of cancer, and increased risk of anesthetic and surgical complications.1,6,10–14 Further, recent studies in a group of age-matched, pair-fed Labrador retrievers show that lean dogs have a significant increase in their median life span (of nearly 2.5 years) and a significant delay in the onset of signs of chronic disease.15 Thus, prevention and early recognition of obesity, as well as correcting obesity when it is present, is essential to appropriate health care, and increases both the quality and quantity of life for pets.

The causes of obesity are multifactorial, and there are many genetic and environmental factors; however, obesity is ultimately related to energy imbalance: too many calories consumed or too few calories burned. Nevertheless, there is increasing evidence that outside factors play an important role in obesity development. One of these recognized factors is breed predisposition to obesity (likely a genetic factor, but this is unproven), and there are clearly other components, such as age, sex, gonadal status, and hormonal influences that play significant roles in the development of obesity. The dog breeds with increased risk of obesity are the Labrador retriever, Boxer,
Cairn terrier, Scottish terrier, Shetland sheepdog, Basset hound, Cavalier King Charles spaniel, Cocker spaniel, Dachshund (especially long-haired), Beagle, and some giant breed dogs. However, some breeds are clearly resistant to development of obesity, with greyhounds being a notable example. In addition to breed-related predisposition, obesity also tends to increase with age. This phenomenon is believed to result from the reduced metabolic rate that occurs with aging. Further, Edney and Smith reported a higher incidence of obesity in dogs with elderly owners, a phenomenon possibly related to food-, behavior-, and exercise-related factors. Obesity is more common in younger female dogs, but as both sexes reach old age (>12 years), 40% of both males and females are obese. Another clear risk factor for obesity is neutering; the incidence of obesity is higher in neutered dogs of both sexes. This problem is believed to be due to hormonal changes associated with neutering and the reduced metabolic rate that occurs with the loss of sex hormones. The reasons for this effect have been studied more in cats, but it is clear that sex hormones (and especially estrogen) are important regulators of energy intake and metabolism. Estrogen recently has been demonstrated to inhibit lipogenesis, and is known to be a determinant of adipocyte number. Thus, changes in sex hormones following neutering seem to influence development of obesity by direct effects on the brain centers affecting satiety and metabolism (eg, the hypothalamus and others), and indirectly by affecting cell metabolism and hormonal regulators of food (eg, ghrelin and leptin). The effect on energy metabolism is significant. A 30% decrease in energy intake was required to prevent post-spay weight gain in female Beagles. In contrast, in a separate study of working dogs, increasing exercise after neutering also resulted in maintenance of ideal body condition compared with dogs that were not neutered. Thus, either a reduction of intake by approximately one-third, or a proportionate increase in exercise, or a combination of both is required to prevent post-neuter weight gain in dogs. This early-age increase in body weight is a significant risk factor for adulthood obesity. As is the case in human childhood obesity, excess weight in puppyhood predisposes dogs to adult obesity, and obese females between 9 and 12 months of age are 1.5 times more likely to become obese as adults. Similar kittenhood obesity study has not been reported in cats, but a similar phenomenon of weight gain following neutering does occur in young cats, predisposing them to early weight gains and the hormonal changes that come with it. Other important risk factors for obesity in dogs are endocrine disorders such as hypothyroidism and hyperadrenocorticism, medications that result in hyperphagia (anticonvulsants and glucocorticosteroids), consumption of table scraps, treats, free-choice feeding or poorly controlled meal feeding, high calorie home-cooked meals, and a sedentary lifestyle that results in a lack of significant exercise.

The goal of the this review is to provide the reader an understanding of the importance of adipose tissue in normal metabolism, and especially in appetite, energy balance, and glucose and fat metabolism. In addition, the role of adipokines, hormones secreted from normal white adipose tissue, are reviewed in both the normal and obese state, giving the reader an insight into the important roles of these hormones in the body. There have been several recent reviews on the nutritional aspects of obesity and the important role of diet and exercise in the management of obesity, so the interested reader is referred to these articles for more information on this aspect of obesity management.

THE ROLE OF ADIPOSE TISSUE IN NORMAL METABOLISM

Adipose tissue has traditionally been considered a diffuse, ill-defined tissue with the primary role of storing energy in the form of triglyceride, and a secondary role as
insulation and protection for other body organs. In actuality, adipose tissue is a much more complex organ and contains a variety of cell types (Fig. 1). In adipose tissues, there are 2 types of adipocytes: white adipose tissue (WAT) and brown adipose tissue. WAT represents the majority of adipocytes in adult tissues and is the familiar image of fat tissue: many large triglyceride-filled cells surrounded by smaller cells and structures. The primary distinction between WAT and brown adipose is the presence of multilocular lipid droplets in brown fat that are actively involved in thermogenesis as a result of expression of distinct genes affecting mitochondrial function, including uncoupling protein-1, and that are found in higher proportions in neonates. Adipose tissue is made up collectively of much more than adipocytes, which account for approximately 50% of the total cell population, but includes pre-adipocytes, multipotent mesenchymal stem cells, endothelial cells, pericytes, macrophages, and nerve cells. The presence of stem cells and pre-adipocytes is crucial to the expansion of adipose tissue that occurs in obesity. These cells are recruited when existing adipocytes reach a critical level of hypertrophy, resulting in adipose tissue hyperplasia. Monocytes and macrophages in adipose tissue have been identified as an important contributors to obesity-related disorders because they are sources of proinflammatory, procoagulant, and acute phase reactant cytokines (adipocytes and endothelial cells also produce these cytokines), and their numbers and activity increase as adipocytes hypertrophy. In addition to understanding adipose tissue as a distinct organ with multiple cell types, research in rats, mice, and humans has shown that fat in different anatomic locations have distinct biologic behavior due to local influences in gene expression and differentiation. In humans, it is clear that the pathologic sequelae of obesity are influenced by the preferential deposition of fat into visceral deposits instead of subcutaneous deposits (Fig. 2). This phenomenon has been termed metabolic syndrome in humans, and is associated with abdominal obesity (accumulation of visceral adipose tissue), blood lipid disorders, inflammation, insulin resistance or type 2 diabetes, and increased risk of developing cardiovascular disease. A difference in secretion of adipokines from regional adipose tissue sites similar to that reported in humans has been reported in cats and dogs, but a true

---

Fig. 1. (A) Light microscopic image of toluidine blue-stained visceral white adipose tissue. Small structures surrounding and interspersed between the triglyceride-filled adipocytes are primarily macrophages and vessels. (B) Electron micrograph of visceral white adipose tissue showing the ultrastructure of the nucleus of an adipocyte with multiple small fat-containing bodies, which are new adipocytes prior to being released. (Courtesy of Mr Ralph Nicholes and Dr Fred Clubb, Texas Heart Institute, Houston, TX.)
metabolic syndrome has not been described in these animals, likely, in part, due to differences in risk factors for cardiovascular disease and blood lipid abnormalities.

An important aspect of adipose tissue function was unknown until the mid-1990s with the discovery that WAT was the source of the hormone leptin. Since that time, WAT has become known as an important endocrine organ that secretes a wide variety of substances, including steroid hormones, growth factors and cytokines, eicosanoids, complement proteins, binding proteins, vasoactive factors, regulators of lipid and glucose metabolism, and others active in energy metabolism and appetite control (Fig. 3).\textsuperscript{30,37–39} The many hormones and factors secreted by adipose tissue have become collectively known as adipokines. Adipokines are essential to normal physiologic function, and are important in the regulation of diverse biologic processes including energy balance, glucose and lipid metabolism, inflammation and immune function, hemostasis, vascular function, and angiogenesis.\textsuperscript{30,40–42} There are more than 50 known adipokines. Of these, the most well known is leptin, but others, such as adiponectin, resistin, and some of the proinflammatory cytokines, for example, interleukins (IL), tumor necrosis factor alpha (TNF\textsubscript{\alpha}), interferon gamma (IFN\textsubscript{\gamma}) and so forth, have been studied in multiple species, including dogs and cats.

**LEPTIN**

Leptin is the prototypical adipokine, and of all of the adipokines is the one best characterized in dogs and cats.\textsuperscript{30,43–45} Leptin is a protein encoded by the \textit{ob} gene, and although adipocytes are the main site of production, leptin mRNA can be found in placenta, mammary gland and liver in humans and rodents.\textsuperscript{45} Although leptin is secreted constitutively by adipocytes, increased secretion is based on the energy flux within these cells, and circulating concentrations of leptin correlate with fat mass.\textsuperscript{46} This correlation is true in all species examined to date, including dogs and cats.\textsuperscript{35,36,47} Transcription of the \textit{ob} gene and secretion of leptin are also controlled by
a variety of metabolic and inflammatory mediators, including insulin, glucocorticoids, endotoxin, and such cytokines as TNFα, IL1β, and IL-6.30,45 The effects of leptin are initiated, as with many adipokines, through interaction with its receptor. The leptin receptor family (Ob-R) is very closely related to members of the IL-6 family of receptors, and although the highest numbers of receptors are expressed in the satiety centers of the hypothalamus, they can be found widely distributed throughout the body, reflecting leptin’s involvement in the regulation of diverse physiologic processes.48–50

When leptin, which is from the Greek “leptos” for thinness, was discovered, its primary actions were believed to be suppression of appetite and increased energy expenditure (via thermogenesis).37,45,49 These early reports were based on mouse models showing that absence of leptin resulted in severe obesity.51 Subsequent studies have shown that leptin binding to its receptor in the hypothalamus results in a series of events leading to suppression of appetite, including stimulation of anorexigenic neurons via neurotransmitters such as cocaine- and amphetamine-regulated transcript (CART), and melanocyte-stimulating hormone (MSH), suppression of orexigenic neurons (via neurotransmitters such as neuropeptide Y and agouti-related peptide), and suppression of the release of endocannabinoids, which are regulators of orexigenic neurons.52–54 Although it is clear that leptin deficiency (either due to lack of the hormone or its receptor) results in development of severe obesity in rodents and humans, it is not a common cause of obesity in humans and has not been documented to date in dogs or cats.55 Rather, the majority of obese humans, and dogs and cats as well, have high circulating concentrations of leptin, and the problem is not leptin deficiency but diminished end-organ response to leptin in the hypothalamus. Thus, obesity unrelated to specific genetic mutations in leptin or its receptor is characterized by leptin resistance and hyperleptinemia. Of note, hyperleptinemia in humans can also occur as a consequence of aging (independent of or disproportional to increases in body fat mass), but this phenomenon has not yet been reported in dogs or cats.56,57 Unfortunately, the causes of leptin resistance are likely multifactorial, which make identification and
reversal of the problem difficult. Also important, leptin resistance results in blunting of the satiety effects of the hormone on the hypothalamus and concurrent lowering of the body’s energy metabolism, thus abetting further weight gain (or at least making weight loss extremely difficult) and predisposing obese subjects to development of other metabolic abnormalities associated with leptin dysfunction. Current research suggests that the blunted response to leptin may be due, at least in part, to saturated transport systems for leptin across the blood-brain barrier or defects in signaling in the hypothalamus, and that leptin resistance is selective: peripheral leptin receptors continue to function and this may be important in the pathogenic metabolic effects of hyperleptinemia in obesity in humans with metabolic syndrome. Leptin is involved in normal reproductive and immune function, and modulation of insulin sensitivity, and generally seems to be proinflammatory (mediated by IL-6 and others), prothrombotic, prooxidant, and has opposite effects to adiponectin. Thus, as with many hormonal and metabolic systems, a balance is achieved between the proinflammatory and anti-inflammatory effects of 2 hormones produced in adipocytes, leptin and adiponectin, and when the balance is disrupted due to development of obesity, it results in hyperleptinemia, leptin resistance, and development of obesity-related disorders.

**Leptin in Dogs and Cats**

Circulating concentrations of leptin correlate with fat mass in both dogs and cats. Thus, increased fat mass, from either experimentally induced obesity or in pet dogs and cats with increased body condition scores, results in predictable, measurable increases in leptin. In contrast, reduction in fat mass also results in a decrease in leptin concentrations in both species. There is ob gene expression in dog pre-adipocytes and mature adipocytes from WAT from multiple sites, but no expression in tissues other than WAT—a finding that has only been observed in the dog. Studies of ob gene expression have not been reported in cats. In both dogs and cats, leptin concentrations are increased after a fatty or high-energy meal. In dogs, this effect can result in 2- to 3-fold increases of leptin concentrations for as long as 8 hours. Of note, in cats the postprandial effect of dietary composition on leptin concentration is not consistent, but seems to be modulated by the relative insulin resistance and body fat mass. Regardless of body condition score and fat mass, cats with insulin resistance (either due to diet or other causes) have higher circulating concentrations of leptin than cats with normal sensitivity to insulin. Thus, the role of leptin in feline metabolism is clearly linked to insulin sensitivity and glucose metabolism. The issue of breed-related influences on metabolism and obesity is unsettled, primarily due to a paucity of published studies; however, results of a recent study by Ishioka and colleagues, show that the breed of dog may influence leptin concentrations. For example, when examined within body condition score groups, Shetland sheepdogs had higher circulating leptin concentrations, whereas dachshunds, Shih Tzu, and Labrador retrievers had lower concentrations. No specific breed-related studies on leptin have been reported in cats. Another factor affecting leptin concentrations in dogs is glucocorticosteroid therapy (eg, dexamethasone increases leptin concentrations in dogs, but prednisone seems to have no effect), and this may also influence feeding status, energy regulation, and other aspects of metabolism. Finally, the effect of neutering on body weight and leptin status in cats has been a topic of considerable interest. In general, increases in leptin occur after neutering in cats, and are correlated with the amount of body fat gained post-neuter, and this effect occurs in both males and females. The increases in leptin likely reflects the strong tendency for cats to gain weight post-neuter if their food intake is not closely regulated. Further studies are required to assess the role of neutering on body fat in cats.
ADIPONECTIN

After leptin, the next most studied and well-understood adipokine is adiponectin. When adiponectin was discovered (after the discovery of leptin in the mid-1990s), a variety of different names were ascribed, including Acrp 30, GBP28, and AdipoQ. Unlike leptin, adiponectin is produced exclusively by mature adipocytes, after which it circulates as trimers, hexamers, or even high molecular weight multimers in very high concentrations. Adiponectin is among the most highly expressed genes in adipose tissue. Adiponectin secretion is stimulated by insulin as well as by several drugs (e.g., thiazolidinediones, and cannabinoid-1 receptor antagonists such as rimonabant) and dietary constituents (e.g., fish oil, linoleic acid, soy protein). These effects have not yet been reported in dogs or cats. Nevertheless, the role of adiponectin is tightly connected to glucose metabolism through enhancing insulin sensitivity and increasing glucose uptake via the GLUT 4 transporter. In addition, adiponectin increases glycolysis by phosphorylation of phosphofructokinase and increases fatty acid oxidation, 2 functions that also are essential to enhanced glucose uptake and metabolism. In humans, other well-characterized effects of include its anti-inflammatory properties (which are opposite of leptin) and inhibition of the development of atherosclerosis. The beneficial cardiovascular effects of adiponectin may stem from its function as a vasodilator, an effect mediated through adiponectin’s promotion of increased expression of endothelial nitric oxide synthase (iNOS) and prostacyclin synthase. The anti-inflammatory effects of adiponectin seem to be due to the ability of the hormone to suppress TNFα production by macrophages. Although these effects are being widely studied in humans, there are no reports yet in dogs or cats confirming similar physiologic effects in these species.

In the obese state, leptin concentrations are typically dramatically increased, reflecting the large increases in fat mass and leptin secretion. However, unlike leptin, increases in fat mass result in decreased concentrations of circulating adiponectin, and conversely, weight loss results in a return to normal adiponectin concentrations. Furthermore, in humans adiponectin concentrations are negatively correlated with body fat mass, fasting insulin concentrations, and plasma triglyceride concentrations. The mechanisms underlying this decrease in adiponectin are unknown, but changes seem to occur at 3 levels: decreased total adiponectin production (which is greatest with visceral adiposity), changes in relative proportions of the molecular weight forms of adiponectin (fewer high molecular weight forms are present in obese individuals), and changes in the expression of adiponectin genes (proinflammatory cytokines IL-6 and TNFα in the enlarging fat mass are inhibitors of these genes). In humans, decreased circulating levels of adiponectin are linked to development of type 2 diabetes, insulin resistance, hypertension, and development of progressive ventricular hypertrophy, and although these syndromes are commonly associated with obesity, the persistent reduction in adiponectin concentrations present even in persons matched for body mass and adiposity suggests that low circulating adiponectin concentration is an independent risk factor for development of metabolic complications.

Adiponectin in Dogs and Cats

Adiponectin nucleotide and amino acid sequences have been determined in both dogs and cats, and show strong homology to those of other species, while canine adiponectin appears to circulate as variably sized complexes similar to human adiponectin. As in humans, both canine and feline adiponectin is highly expressed in WAT, and in cats the gene is expressed in significantly greater amounts in visceral adipose sites. Similar to humans, both dogs and cats have lower circulating concentrations
of adiponectin with increased fat mass, and in dogs the gene expression is also decreased (this is not yet been studied in cats). Studies in dogs and cats indicate that adiponectin is predictably decreased in the obese state, suggesting that this hormone may have similar roles in the development of the metabolic changes, insulin resistance, and type 2 diabetes. Further work is needed to define the role of adiponectin in the development of feline diabetes, the incidence of which has greatly increased in recent years.

**RESISTIN**

Resistin was originally discovered as an adipokine secreted by murine adipocytes. This hormone is also found in human adipocytes, as well as in adipose tissues of cattle and pigs. To date, expression of resistin has not been documented in dog or cat adipocytes, but the technical issues of assay development have been profound, and this may have slowed this discovery. In addition, the resistin receptor has also not yet been found. Thus, a great deal of work is needed to further define the presence and role of this adipokine in domestic animals and humans. However, the secretion of this hormone in rodents seems to follow leptin: circulating concentrations increase with increasing fat mass and following a meal. Hyperresistinemia results in development of insulin resistance and metabolic derangements typical of type 2 diabetes. Increased concentrations of resistin are associated with proinflammatory cytokine secretion by macrophages, and in humans, increased resistin concentrations are correlated with atherosclerosis. Additional work is required to fully understand the role of this adipokine in obesity-related disorders, especially those associated with dysregulation of glucose and development of insulin resistance.

**ANGIOTENSINOGEN AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM**

One of the best known metabolic/regulatory systems in the body is the renin-angiotensin-aldosterone system (RAAS), and its importance in vascular homeostasis, water balance, and renal function is well documented. Thus, the recognition that RAAS plays an important role in normal adipocyte biology, and particularly in adipocyte differentiation and metabolism, was a crucial discovery. WAT is a major source of angiotensinogen in humans and rodents, second only to the liver in concentrations of this precursor to angiotensin II. In fact, renin and angiotensin-converting enzyme are present in high concentrations in fat as well, and the local production of angiotensin II in adipose tissue seems to play a role in normal adipocyte differentiation, size, and insulin sensitivity. In obese humans, increased production of angiotensinogen is a major contributor to the development of cardiovascular and kidney disease. Increases in angiotensinogen from adipocytes result in increased circulating concentrations of angiotensin II, which promotes increased vasoconstrictor activity (which can lead to hypertension or renal dysfunction), and increased concentrations of aldosterone, which promotes renal sodium retention. Studies in obese rodents show that dysregulation of the RAAS system ultimately leads to reduced renal blood flow and glomerular filtration as well as to development of hypertension, both potentially very harmful to kidney function and development of renal disease. As with resistin, the role of the RAAS system in adipocytes and in obesity in dogs and cats is not well understood. Only one study has documented the activation of the RAAS in diet-induced obesity in dogs, and in that study the focus was on the effects of RAAS activation on functional and structural changes in the kidney as a model of human disease. Based on the importance of RAAS in obesity-associated diseases in humans and rodents, the role of RAAS in obese dogs and cats may also be important.
INFLAMMATORY CYTOKINES (INTERLEUKINS, TNF-α, CHEMOTACTIC AND COMPLEMENT PROTEINS)

Obesity is considered to be a chronic inflammatory disease. In humans, the inflammation associated with obesity is known to cause insulin resistance, dyslipidemia (increased plasma triglycerides, decreases in high-density lipoprotein [HDL]-cholesterol, increases in low-density lipoprotein [LDL]-cholesterol), heart diseases (including atherosclerosis, hypertrophic cardiomyopathy, and heart failure secondary to the increased preload and afterload as a result of hypertension and fat mass), increased risk of hypertension and stroke, and osteoarthritis.103–106 In normal-weight individuals, concentrations of proinflammatory cytokines secreted by adipose tissues are low or undetectable. However, in obesity, adipokine production is dysregulated, resulting in increased production of proinflammatory cytokines, while increased numbers of macrophages, which also secrete cytokines that promote the inflammatory process, are recruited to adipose tissue.103 Although a wide variety inflammatory cytokines are produced by adipose tissue, TNF-α and IL6 are the most widely studied cytokines produced by adipose tissue in any species, including dogs and cats.30,39 TNF-α was originally named for its ability to induce the necrosis of cancers after acute bacterial infection. However, this cytokine is actively involved in many processes, including inflammation, autoimmune diseases, tumorigenesis, viral replication, septic shock, fever, and obesity.39,105,106 TNF-α was first shown to be involved in adipocyte metabolism by suppressing the expression of many adipose-specific genes, such as lipoprotein lipase, and by stimulating lipolysis.107 More recently, TNF-α was found to have an important role in the development of insulin resistance as a result of its ability to downregulate GLUT 4 in adipose tissue.108 Subsequent studies in rodents have proven a role of TNF-α in the development of insulin resistance, but human studies attempting to neutralize the effects of the cytokine have shown less compelling improvements in insulin sensitivity. Thus, the complete role of this cytokine in the development of insulin resistance remains to be discovered. The interleukins, and specifically IL6, seem to have a significant role in obesity-associated inflammation in all species studied to date. In humans, serum concentrations of IL-6 are increased in type 2 diabetes and in metabolic syndrome, and correlate with an increase in body fat mass.39 Some of the effects of IL-6 secreted from adipocytes include stimulation of hepatic triglyceride secretion, inhibition of insulin signaling in hepatocytes, and induction of hepatic C-reactive protein synthesis.28,39 WAT is also a source of a variety of other inflammatory cytokines, including IFN-γ, other interleukins (IL-1, -8, -10, -18), C-reactive protein, monocyte chemotactic protein-1, and complement proteins, such as platelet activator inhibitor-1, Factor VII, and tissue factor (see Fig. 2).28,37,39,108,110 In short, the chronic, subacute state of inflammation that accompanies the accumulation of WAT has been documented by the increases in circulating concentrations of inflammatory markers, and is further evidence that obesity-induced inflammation plays an important pathogenic role in the development and progression of obesity-related disorders.

INFLAMMATORY ADIPOKINES IN DOGS AND CATS

Studies in dogs have only recently begun to document the role of proinflammatory cytokines in the pathogenesis of obesity and obesity-related disorders in this species. Using reverse transcription-polymerase chain reaction to detect the mRNA of adipokines in dog adipocytes, investigators have detected genes for angiotensinogen, plasminogen activator inhibitor-1, IL-6, haptoglobin, metallothionein-1 and -2, and nerve growth factor in adipocytes of WAT.37 Other investigators, in a study of experimentally induced obesity in dogs, reported increases in TNF-α, insulin-like growth factor, and
nonesterified fatty acids that were found concurrently with increased body fat mass and decreased insulin sensitivity. Both of these studies mirror results in human and rodent studies, and suggest that obesity in dogs has many of the same physiologic and pathologic characteristics previously described in these species. Another study in obese dogs found that although the dogs developed biochemical evidence of insulin resistance, instead of having increased concentrations of C-reactive protein, concentrations were decreased significantly. This finding contrasts with those of studies in humans in which C-reactive protein concentrations increase in obesity. Finally, studies of proinflammatory cytokines in feline obesity are lacking.

UNDERSTANDING OBESITY AS A DISEASE

Obese humans generally do not live as long as their lean counterparts, and are much more likely to suffer from obesity-related diseases. Dogs and cats are susceptible to the same detrimental effects, including decreased longevity, and development of a variety of disorders that are also associated with human obesity (Box 1). Dietary calorie restriction to maintain a lean body condition significantly increased longevity in a group of 24 Labrador retrievers. In that study, the dogs in the energy-restricted group were fed approximately 25% less than their pair-fed counterparts (another group of 24 dogs), which were allowed to become overweight or obese. The lean dogs lived an average of 2 years longer than their overweight counterparts, and had reduced incidences of hip dysplasia, osteoarthritis, and glucose intolerance as well. This study and others illustrate that obesity is clearly associated with increased morbidity (in this study morbidity was associated with osteoarthritis) and early mortality. Heat intolerance, increased anesthetic risk, increased difficulty with routine clinical procedures (catheter placement, palpation, imaging), and prolonged surgical procedures have also been documented in obese dogs. Until recently, however, there were few studies in dogs, and even fewer in cats, that illustrated the increased disease risk associated with obesity.

As in humans, obesity in dogs and cats is associated with a variety of endocrine abnormalities. The most widely recognized and studied example is insulin resistance and the increased risk of development of type 2 diabetes. The problem of obesity-induced insulin resistance is increasing in cats concurrent with the increase in type 2 diabetes in cats over the past 10 years. In dogs, however, subclinical glucose intolerance and insulin resistance is often present without overt signs of diabetes. In addition to the hormonal effects of obesity on insulin function, there is an increasing body of evidence showing that obesity has a profound effect on thyroid hormone function. In one study, 42% of obese dogs had biochemical evidence of hypothyroidism (low serum free T4 [fT4] concentrations, high serum thyrotropin [TSH] concentrations, or both), and of these dogs, a large percentage had no other clinical signs of hypothyroidism (similar to a phenomenon in humans termed subclinical hypothyroidism, in which TSH is increased and T4 is either normal or decreased). However, in an earlier study assessing the role of thyroid hormone in canine obesity, the only differences observed were in total T4 and total T3 concentrations, which were higher in the obese dogs. This may occur as a result of thyroid hormone resistance, but no studies support this. Of note, in a study of obese cats, fT4 concentrations increased significantly (some increases were within the normal range), and the increase was proportional to the increase in nonesterified fatty acids (NEFAs) (free fatty acids increase in feline obesity), a finding that may indicate that thyroid hormone uptake at the cellular level is inhibited by the presence of high concentrations of NEFAs. Further clarification of the effects of obesity on thyroid hormone function is needed before specific
recommendations can be made; however, obesity seems to have a significant influence on thyroid hormones and their cellular function.

Dyslipidemias (alterations in cholesterol, triglycerides, and NEFAs) are commonly associated with obesity in humans, and in fact are one of the components of the metabolic syndrome. To date, only a few studies have been performed in either dogs or cats that further define changes in serum lipids in these species. However, one

<table>
<thead>
<tr>
<th>Box 1 Disorders associated with obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orthopedic disorders</strong></td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Fractures (primarily humeral condyles)</td>
</tr>
<tr>
<td>Cruciate ligament tears/rupture</td>
</tr>
<tr>
<td>Intervertebral disk disease</td>
</tr>
<tr>
<td>Joint disorders</td>
</tr>
<tr>
<td><strong>Endocrine and metabolic disorders</strong></td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Glucose intolerance</td>
</tr>
<tr>
<td>Hepatic lipodosis (cats)</td>
</tr>
<tr>
<td><strong>Cardiac and respiratory disorders</strong></td>
</tr>
<tr>
<td>Pickwickian syndrome</td>
</tr>
<tr>
<td>Tracheal collapse</td>
</tr>
<tr>
<td>Laryngeal paralysis</td>
</tr>
<tr>
<td>Brachycephalic airway syndrome</td>
</tr>
<tr>
<td>Reduced airway compliance</td>
</tr>
<tr>
<td><strong>Urogenital disorders</strong></td>
</tr>
<tr>
<td>Urolithiasis (calcium oxalate)</td>
</tr>
<tr>
<td>Urethral sphincter mechanism incompetence</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Mammary neoplasia</td>
</tr>
<tr>
<td>Dystocia</td>
</tr>
<tr>
<td>Idiopathic cystitis</td>
</tr>
<tr>
<td><strong>Other miscellaneous disorders</strong></td>
</tr>
<tr>
<td>Heat intolerance</td>
</tr>
<tr>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>Increased anesthetic risk</td>
</tr>
<tr>
<td>Reduced life span</td>
</tr>
</tbody>
</table>
cross-sectional study in dogs evaluated the effect of obesity on serum concentrations of glucose, cholesterol, HDL-cholesterol, triglyceride, and alanine aminotransferase activity, and found that significant increases in serum triglycerides and total cholesterol occurred in obese dogs. These findings were confirmed in another clinical study assessing the utility of a bioelectric impedance device for assessment of body fat in dogs. In that study, serum cholesterol and triglyceride concentrations were also significantly higher in obese dogs than in lean dogs. Another study of cats fed to achieve long-term obesity revealed similar changes in plasma lipids similar to those seen in obese people. Obese cats had increased NEFAs and triglycerides, decreased HDL, increased LDL, and total increases in total cholesterol, and these changes occurred irrespective of diet. In both dogs and cats, obesity seems to cause significant changes in lipid and lipoprotein metabolism that may be important in the development of other obesity-associated diseases.

Obese humans are prone to development of a variety of respiratory syndromes and airway distress, ranging from increased episodes of asthma to difficulty breathing due to Pickwickian-type obstruction of thoracic movement. Few reports of similar conditions have appeared that address the effects of obesity on respiratory function in dogs or cats. However, there have been widespread anecdotal reports of obesity creating greater distress for dogs with tracheal collapse, laryngeal paralysis, and cats with asthma, suggesting a possible association. More evidence of the deleterious effects of obesity on the respiratory system have recently begun to surface, with the observations that obesity causes expiratory airway dysfunction in dogs. In that study, normal breathing was unaffected by body condition, but in obese dogs (body condition score 9/9) during hyperpnea, expiratory airway resistance was markedly greater, indicating a dynamic flow limitation in these dogs that likely occurs in the distal airways. No other abnormalities in airway function were observed. Further studies are needed to determine whether these changes are due to increases in inflammatory cytokines from obesity or due to airway wall resistance from decreased compliance. In either case, this study demonstrates that airway dysfunction, though subclinical in the majority of dogs, can occur. Studies of respiratory function in obese cats have not been published.

**TREATMENT OF OBESITY**

The management of obesity in dogs has long been focused on reducing energy consumption (dietary management) and increasing energy expenditure (exercise). This therapeutic approach is very effective when it is implemented completely and early, however, it can be quite difficult to overcome the behavioral, social, metabolic, and hormonal influences of obesity in many dogs and cats. In humans, obesity management options include dietary management, exercise, behavior modification, pharmacologic therapy, and surgery. At this point, surgical therapy for obesity in dogs and cats has not been reported. For cats, there are currently no safe pharmacologic treatments for obesity, and until recently the options for dogs were limited to those products that reduced intestinal absorption of fat—a less than ideal approach with a significant therapeutic downside—and drugs that increased sympathetic tone, and were generally ineffective or potentially harmful.

Dirlotapide (Slentrol) is a newer drug that is effective in treatment of obesity in dogs. The drug is a selective (intestinal) microsomal triglyceride transfer protein (MTP) inhibitor. Dirlotapide reduces the absorption of fat from the small intestine by slowing the packaging of fatty acids and protein into chylomicrons, a process driven by MTP activity in the cytoplasm of the enterocyte. As a result of MTP inhibition, there is
a reduction in fat absorption from the small intestinal lumen, but this is responsible for only a small fraction (approximately 10%) of the effect of dirlotapide on weight loss. Further, because the fat is absorbed into the enterocyte, steatorrhea and other side effects related to fat malabsorption are minimal. Intracellular accumulation of fat due to MTP inhibition triggers release of peptide YY from the enterocyte into the systemic circulation. Peptide YY is a potent appetite suppressant and satiety hormone, and is one of the peripheral hormones responsible for signaling the hypothalamus and other brain centers to control intake. The primary effect of dirlotapide is reduction in appetite. In clinical trials and in client-owned dogs, dirlotapide typically causes a reduction in food intake of about 10%. The key benefit of adding dirlotapide to a weight loss program is that it influences one of the major obstacles to successful weight loss: it helps to control food intake. And although it is important to recognize that successful management of obesity requires appropriate dietary and exercise regimens, dirlotapide can be an effective tool in to the treatment of obesity.

SUMMARY

Obesity is the most common nutritional disorder of dogs and cats in Western countries. Although obesity is caused by an imbalance between energy intake and energy expenditure, there are many factors, both environmental and genetic, that influence this balance. Further, the alarming increase in obesity is important because this condition is associated with important metabolic and hormonal changes in the body. The systemic metabolic and hormonal changes that occur in obesity are the result of dysregulation of the adipokines secreted by WAT, and are the key factors in many diseases and disorders associated with obesity. The list of conditions associated with obesity is increasing as new research identifies the relationships between proinflammatory adipokines and disorders such as osteoarthritis, respiratory distress, diabetes mellitus, hypertension, dystocia, heat intolerance, and some forms of cancer. Because of the seriousness of obesity as a metabolic, hormonal, and inflammatory disease, prevention and management of obesity is essential.

REFERENCES

106. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation and insulin resistance. Eur Cytokine Netw 2006;17:4–12.
115. Smith GK, Mayhew PD, Kapatkin AS, et al. Evaluation of risk factors for degenerative joint disease in association with hip dysplasia in German shepherd dogs,


