Obesity in Dogs and Cats: A Metabolic and Endocrine Disorder

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KEYWORDS

• Obesity • Adipocytes • Adipokines • Leptin • Adiponectin
• Cytokines • Dog • Cat

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,

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Cairn terrier, Scottish terrier, Shetland sheepdog, Basset hound, Cavalier King Charles spaniel, Cocker spaniel, Dachshund (especially long-haired), Beagle, and some giant breed dogs.[3,6,16,17] However, some breeds are clearly resistant to development of obesity, with greyhounds being a notable example.[17] 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.[18] Further, Edney and Smith[6] 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.[5,19–21] 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.[5,6,22] 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.[23] 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).[17,24,25] The effect on energy metabolism is significant. A 30% decrease in energy intake was required to prevent post-spay weight gain in female Beagles.[25] 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.[26] 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.[20] 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.[3,17,22]

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.[2,4,27]

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.[28,29] 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.[30] 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.[31] 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.[28] 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.[32] 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**).[28,32] 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.[33,34] A difference in secretion of adipokines from regional adipose tissue sites similar to that reported in humans has been reported in cats and dogs,[35,36] but a true

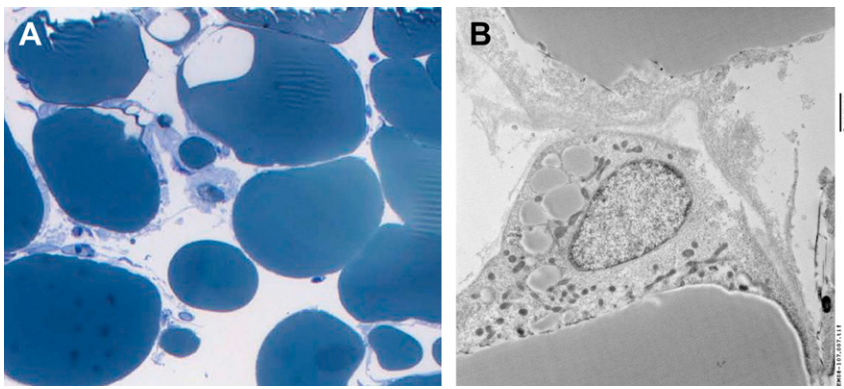

Fig. 1. (*A*) Light microscopic image of toluidine blue-stained visceral white adipose tissue. Small structures surrounding and interspersed between the triglyceride-filled adipocytes are primarily macrophages and vessels. (*B*) Electron micrograph of visceral white adipose tissue showing the ultrastructure 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.)

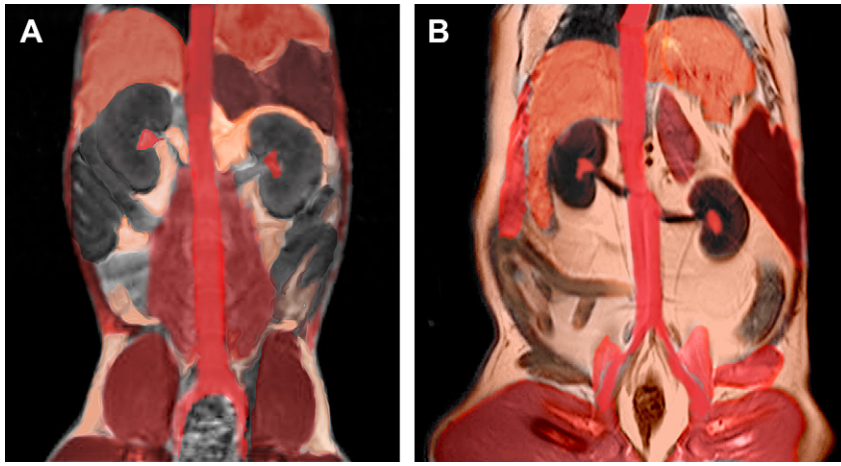

Fig. 2. (*A*) Magnetic resonance image (T1-weighted) of a normal dog (body condition score 4/9) illustrating the normal structures and small amount of intra-abdominal body fat. (*B*) Magnetic resonance image (T1-weighted) of an obese dog (body condition score 8/9) illustrating the large amounts of intra-abdominal fat. The image has been colorized to improved visualization of organs versus adipose. (*Courtesy of* Washington State University College of Veterinary Medicine, Pullman, WA; with permission.)

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**).[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.[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 (TNFα), interferon gamma (IFNγ) 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.[30,43–45] Leptin is a protein encoded by the *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.[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.[46] This correlation is true in all species examined to date, including dogs and cats.[35,36,47] Transcription of the *ob* gene and secretion of leptin are also controlled by

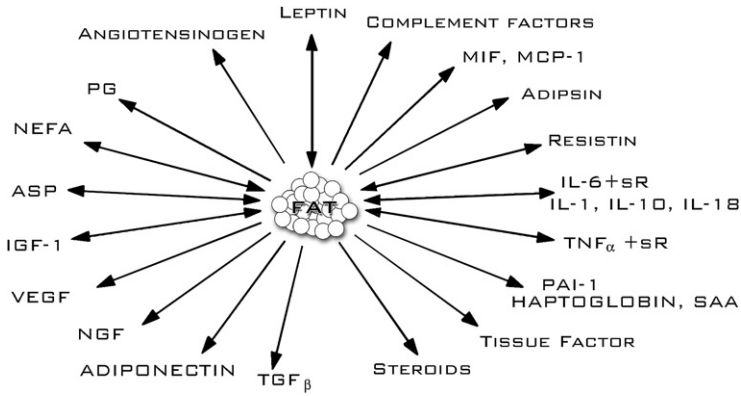

Fig. 3. Illustration of white adipose tissue (WAT) adipocytes showing and some of the hormones and cytokines secreted by this tissue. This illustration is not representative of all adipocytokines known to be produced by WAT. ASP, acylation stimulating protein; IGF, insulin-like growth factor; MCP, monocyte chemotactic protein; MIF, macrophage inhibitory factor; NGF, nerve growth factor; PAI, platelet activator inhibitor; PG, prostaglandin; sR, serine receptor; SAA, serum amyloid A; TGF, tumor growth factor; VEGF, vascular endothelial growth factor. (Illustration by Mr Larry Wadsworth, Texas A&M University, College Station, TX.)

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,[42] 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.[58,59] 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.[60–66] 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.[35,61] 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.[67] 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.[68] 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.[69,70] 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.[71] 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,[62] 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.[62] 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.[60,72] 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.[65,73,74] 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.[75] 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.[75] Adiponectin secretion is stimulated by insulin as well as by several drugs (eg, thiazolidinediones, and cannabinoid-1 receptor antagonists such as rimonabant) and dietary constituents (eg, fish oil, linoleic acid, soy protein).[76–78] 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.[79–81] 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.[81] In humans, other well-characterized effects of include its anti-inflammatory properties (which are opposite of leptin) and inhibition of the development of atherosclerosis.[82] 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.[83,84] The anti-inflammatory effects of adiponectin seem to be due to the ability of the hormone to suppress TNFα production by macrophages.[85] 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.[86] Furthermore, in humans adiponectin concentrations are negatively correlated with body fat mass, fasting insulin concentrations, and plasma triglyceride concentrations.[87] 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).[30,88] In humans, decreased circulating levels of adiponectin are linked to development of type 2 diabetes, insulin resistance, hypertension, and development of progressive ventricular hypertrophy,[89,90] 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,[91–93] 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.[93] 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).[35,47,92] 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.[94–96] 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.[97,98] Increased concentrations of resistin are associated with proinflammatory cytokine secretion by macrophages, and in humans, increased resistin concentrations are correlated with atherosclerosis.[99] 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.[30] WAT is a major source of angiotensinogen in humans and rodents, second only to the liver in concentrations of this precursor to angiotensin II.[100] 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.[100,101] 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.[100–102] 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.[100–102] 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.[102] 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, TNFα, 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, TNFα and IL6 are the most widely studied cytokines produced by adipose tissue in any species, including dogs and cats.[30,39] TNFα 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] TNFα was first shown to be involved in adipocyte metabolism by suppressing the expression of many adiposespecific genes, such as lipoprotein lipase, and by stimulating lipolysis.[107] More recently, TNFα 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 TNFα 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**).[28,37,39,109,110] 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 TNFα, insulin-like growth factor, and

nonesterified fatty acids that were found concurrently with increased body fat mass and decreased insulin sensitivity.[47] 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.[111] 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.[112–114] 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**).[1] Dietary calorie restriction to maintain a lean body condition significantly increased longevity in a group of 24 Labrador retrievers.[15] 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.[11,15,115] 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.[1,27] 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.[35,47] 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.[71] 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 $T_{4\ (fT4)}$ 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 T_4 is either normal or decreased).[76] However, in an earlier study assessing the role of thyroid hormone in canine obesity, the only differences observed were in total T_4 and total T_3 concentrations, which were higher in the obese dogs.[116] This may occur as a result of thyroid hormone resistance, but no studies support this. Of note, in a study of obese cats, fT_4 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.[117] Further clarification of the effects of obesity on thyroid hormone function is needed before specific

Box 1
Disorders associated with obesity

Orthopedic disorders
Osteoarthritis
Fractures (primarily humeral condyles)
Cruciate ligament tears/rupture
Intervertebral disk disease
Joint disorders

Endocrine and metabolic disorders
Hyperadrenocorticism
Hypothyroidism
Diabetes mellitus
Hypopituitarism
Hyperlipidemia
Glucose intolerance
Hepatic lipidosis (cats)

Cardiac and respiratory disorders
Pickwickian syndrome
Tracheal collapse
Laryngeal paralysis
Brachycephalic airway syndrome
Reduced airway compliance

Urogenital disorders
Urolithiasis (calcium oxalate)
Urethral sphincter mechanism incompetence
Transitional cell carcinoma
Mammary neoplasia
Dystocia
Idiopathic cystitis

Other miscellaneous disorders
Heat intolerance
Exercise intolerance
Increased anesthetic risk
Reduced life span

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

cross-sectional study in dogs evaluated the effect of obesity on serum concentrations of glucose, cholesterol, HDL-cholesterol, triglyceride, and on alanine aminotransferase activity, and found that significant increases in serum triglycerides and total cholesterol occurred in obese dogs.[118] 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.[119] 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 overall increases in total cholesterol, and these changes occurred irrespective of diet.[120] 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.[121,122] 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.[14] 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.[14] 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[2,4]; 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.[3]

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.[123] 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.[124] 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.[124] 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 a causes reduction in food intake of about 10%.[123] 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

1. German AJ. The growing problem of obesity in dogs and cats. J Nutr 2006;136: 1940S–6S.
2. German AJ, Holden SL, Bissot T, et al. Dietary energy restriction and successful weight loss in obese client-owned dogs. J Vet Intern Med 2007;21:1174–80.
3. Gossellin J, Wren JA, Sunderland SL. Canine obesity: an overview. J Vet Pharmacol Ther 2007;30(Suppl 1):1–10.
4. Laflamme DP. Understanding and managing obesity in dogs and cats. Vet Clin North Am Small Anim Pract 2006;36:1283–95.
5. McGreevy PD, Thomson PC, Pride C, et al. Prevalence of obesity in dogs examined by Australian veterinary practices and the risk factors involved. Vet Rec 2005;156:696–707.
6. Edney AT, Smith PM. Study of obesity in dogs visiting veterinary practices in the United Kingdom. Vet Rec 1986;118:391–6.
7. Crane SW. Occurrence and management of obesity in companion animals. J Small Anim Pract 1991;32:275–82.
8. Kronfeld DS, Donoghue S, Glickman LT. Body condition and energy intakes of dogs in a referral teaching hospital. J Nutr 1991;121(Suppl 11):S157–8.

9. Lund EM, Armstrong PJ, Kirk CK, et al. Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999;214:1336–41.
10. Fettman MJ, Stanton CA, Banks I, et al. Effects of neutering on body weight, metabolic rate and glucose tolerance in domestic cats. Res Vet Sci 1997;62: 131–6.
11. Kealy RD, Lawler DF, Ballam JM, et al. Evaluation of the effect of limited food consumption on radiographic evidence of osteoarthritis in dogs. J Am Vet Med Assoc 2000;217:1678–80.
12. Burkholder WJ. Precision and practicality of methods assessing body composition of dogs and cats. Comp Cont Ed Pract Vet 2001;23:1–10.
13. Montoya JA, Morris PJ, Bautista I, et al. Hypertension: a risk factor associated with weight status in dogs. J Nutr 2006;136:2011S–3S.
14. Bach JF, Rozanski EA, Bedenice D, et al. Association of expiratory airway dysfunction with marked obesity in healthy dogs. Am J Vet Res 2007;68:670–5.
15. Kealy RD, Lawler DF, Ballam JM, et al. Effect of diet restriction on life span and age-related changes in dogs. J Am Vet Med Assoc 2002;220:1315–20.
16. Meyer H, Drochner W, Weidenhaupt C. [A contribution to the occurrence and treatment of obesity in dogs]. Dtsch Tierarztl Wochenschr 1978;85:133–6 [in German].
17. Diez M, Nguyen P. The epidemiology of canine and feline obesity. Waltham Focus 2006;16:2–8.
18. Robertson ID. The association of exercise, diet and other factors with owner perceived obesity in privately owned dogs from metropolitan Perth, WA. Prev Vet Med 2003;58:75–83.
19. Sloth C. Practical management of obesity in dogs and cats. J Small Anim Pract 1992;33:178–82.
20. Glickman LT, Sonnenschein EG, Goickman NW, et al. Pattern of diet and obesity in female adult pet dogs. Vet Clin Nutr 1995;2:6–13.
21. Armstrong PJ, Lund EM. Changes in body composition and energy balance with aging. Vet Clin Nutr 1996;3:83–7.
22. Jeusette I, Detilleaux J, Cuvelier C, et al. Ad libitum feeding following ovariectomy in female Beagle dogs: effect on maintenance energy requirement and on blood metabolites. J Anim Physiol Anim Nutr 2004;88:117–21.
23. Cooke PS, Naaz A. Role of estrogens in adipocyte development and function. Exp Biol Med 2004;229:1127–35.
24. Houpt KA, Hintz HF. Obesity in dogs. Canine Pract 1978;5:54–8.
25. Jeusette I, Lhoest ET, Istasse L, et al. Influence of obesity on plasma lipid and lipoprotein concentrations in dogs. Am J Vet Res 2007;68.
26. LeRoux PH. Thyroid status, oestradiol level, work performance and body mass of ovariectomised bitches. J S Afr Vet Assoc 1983;54:115–7.
27. Blanchard G, Nguyen P, Gayet C, et al. Rapid weight loss with a high-protein low-energy diet allows the recovery of ideal body composition and insulin sensitivity in obese dogs. J Nutr 2004;134:2148S–50S.
28. Lafontan M. Fat cells: afferent and efferent messages define new approaches to treat obesity. Annu Rev Pharmacol 2005;45:119–46.
29. Rousset S, Alves-Guerra MC, Mozo J, et al. The biology of mitochondrial uncoupling proteins. Diabetes 2004;53:S130–5.
30. Radin MJ, Sharkey LC, Holycross BJ. Adipokines: a review of biological and analytical principles and an update in dogs, cats, and horses. Vet Clin Pathol 2009;38:136–56.

31. Fischer-Posovaszky P, Wabistsch M, Hochberg Z. Endocrinology of adipose tissue—an update. Horm Metab Res 2007;39:314–21.
32. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21:697–738.
33. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.
34. Fernandez ML. The metabolic syndrome. Nutr Rev 2007;65:S30–4.
35. Hoenig M, Caffail Z, Ferguson DC. Triiodothyronine differentially regulates key metabolic factors in lean and obese cats. Domest Anim Endocrinol 2007;34:229–37.
36. Leray V, Serisier S, Khosniat S, et al. Adipose tissue gene expression in obese dogs after weight loss. J Anim Physiol Anim Nutr 2008;92:390–8.
37. Badman MK, Flier JS. The adipocytes as an active participant in energy balance and metabolism. Gastroenterologist 2007;132:2103–15.
38. Rosen ED, Spiegelman B. Adipocytes as regulators of energy balance and glucose homeostasis. Nature 2006;444:847–52.
39. Juge-Aubry CE, Henrichot E, Meier CA. Adipose tissue: a regulator of inflammation. Best Pract Res Clin Endocrinol Metab 2005;19:547–66.
40. Lago F, Dieguez C, Gomez-Reino J, et al. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716–24.
41. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab 2004;89:2563–8.
42. Pan W, Kastin AJ. Adipokines and the blood brain barrier. Peptides 2007;28: 1317–30.
43. Iwase M, Kimura K, Sasaki N, et al. Canine leptin: cDNA cloning, expression and activity of recombinant protein. Res Vet Sci 2000;68:109–14.
44. Sakaki N, Shibata H, Honjoh T, et al. cDNA cloning of feline leptin and its mRNA expression in adipose tissue. J Vet Med Sci 2001;63:1115–20.
45. Harris RBS. Leptin: much more than a satiety signal. Annu Rev Nutr 2000;20: 45–75.
46. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive leptin concentrations in normal weight and obese humans. N Engl J Med 1996;334:292–5.
47. Gayet C, Baihache E, Dumon H, et al. Insulin resistance and changes in plasma concentrations of TNFα, IGF1, and NEFA in dogs during weight gain and obesity. J Anim Physiol Anim Nutr 2004;88:157-65.
48. Tartaglia LA, Dembski M, Weng X, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83:1263–71.
49. Houseknecht LK, Portocarrero CP. Leptin and its receptors: regulators of whole body energy homeostasis. Domest Anim Endocrinol 1998;15:457–75.
50. Baumann H, Morella KK, White DW, et al. The full-length leptin receptor has signaling capabilities of interleukin 6-type receptors. Proc Natl Acad Sci U S A 1996;93:8374–8.
51. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32.
52. Ahima RS, Prabakaran D, Mantzoros CS, et al. Role of leptin in the neuroendocrine response to fasting. Nature 1996;382:250–2.
53. Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature 2001;411: 480–4.
54. Balthasar N, Coppari R, McMinn J, et al. The hypothalamic arcuate nucleus: a key site for mediating leptin's effects on glucose homeostasis and locomotor activity. Cell Metab 2005;1:63–72.

55. Farooqui IS, Wangensteen T, Collins S, et al. Clinical and molecular genetic spectrum of congential deficiency of the leptin receptor. N Engl J Med 2007; 356:237–47.
56. Gabriely N, Ma XH, Yang XM, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging. Diabetes 2002;51:2951–8.
57. Wang Y. Cross-national comparison of childhood obesity: the epidemic and the relationship between obesity and socioeconomic status. Int J Epidemiol 2001; 30:1129–36.
58. Margetic S, Gazzola C, Regg GG, et al. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord 2002;26:1407–33.
59. Correia MLG, Rahmouni K. Role leptin in the cardiovascular and endocrine complications of metabolic syndrome. Diabetes Obes Metab 2006;8:603–10.
60. Ishioka K, Soliman MM, Sagawa M, et al. Experimental and clinical studies on plasma leptin in obese dogs. J Vet Med Sci 2002;64:349–53.
61. Jeusette IC, Lhoest ET, Istasse LP, et al. Influence of obesity on plasma lipid and lipoprotein concentrations in dogs. Am J Vet Res 2005;66:81–6.
62. Ishioka K, Hosoya K, Kitagawa H, et al. Plasma leptin concentration in dogs: effects of body condition score, age, gender, and breeds. Res Vet Sci 2007; 82:11–5.
63. Backus RC, Havel PJ, Gingerich RL, et al. Relationship between serum leptin immunoreactivity and body fat mass as estimated by use of a novel gas-phase Fourier transform infrared spectroscopy deuterium dilution method in cats. Am J Vet Res 2000;61:796–801.
64. Appleton DJ, Rand JS, Sunvold GD. Plasma leptin concentrations in cats: Reference range, effect of weight gain and relationship with adiposity as measured by dual energy x-ray absorptiometry. J Feline Med Surg 2000;2:191–9.
65. Martin L, Siliart B, Dumon H, et al. Leptin, body fat content and energy expenditure in intact and gonadectomized adult cats: a preliminary study. J Anim Physiol Anim Nutr 2001;85:195–9.
66. Hoenig M, Ferguson DC. Effects of neutering on hormonal concentrations and energy requirements in male and female cats. Am J Vet Res 2002;63:634–9.
67. Eisele I, Wood IS, German AJ, et al. Adipokine gene expression in dog adipose tissues and dog white adipocytes differentiated in primary culture. Horm Metab Res 2005;37:474–81.
68. Ishioka K, Hatai H, Komabayashi K, et al. Diurnal variations of serum leptin in dogs: effects of fasting and re-feeding. Vet J 2005;169:85–90.
69. Thiess S, Becskei C, Tomsa K, et al. Effects of high carbohydrate and high fat diet on plasma metabolite levels and on IV glucose tolerance test in intact and neutered male cats. J Feline Med Surg 2004;6:207–18.
70. Backus RC, Cave NJ, Keisler DH. Gonadectomy and high dietary fat but not high dietary carbohydrate induce gains in body weight and fat of domestic cats. Br J Nutr 2007;98:641–50.
71. Appleton DJ, Rand JS, Sunvold GD. Plasma leptin concentrations are independently associated with insulin sensitivity in lean and overweight cats. J Feline Med Surg 2002;4:83–93.
72. Nishii N, Takasu M, Ohba Y, et al. Effects of administration of glucocorticoids and feeding status on plasma leptin concentrations in dogs. Am J Vet Res 2006;67:266–70.
73. Belsito KR, Vester BM, Keel T, et al. Impact of ovariohysterectomy and food intake on body composition, physical activity, and adipose gene expression in cats. J Anim Sci 2009;87:594–602.

74. Martin LJM, Siliart B, Dumon H, et al. Spontaneous hormonal variations in male cats following gonadectomy. J Feline Med Surg 2006;8:309–14.
75. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439–51.
76. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases ACRP30 mRNA in adipose tissue of obese fa/fa rats and in cultured adipocytes cells. Mol Pharmacol 2003;63:908–14.
77. Rossi AS, Lombardo YB, Lacorte JM, et al. Dietary fish oil positively regulates plasma leptin and adiponectin levels in sucrose fed, insulin resistant rats. Am J Physiol Regul Integr Comp Physiol 2005;289:R486–94.
78. Nagasawa A, Fukui K, Kojima M, et al. Divergent effects of soy protein diet on the expression of adipocytokines. Biochem Biophys Res Commun 2003;311:909–14.
79. Pajvani UB, Du X, Combs TP, et al. Structure-function studies of the adipocyte-secreted hormone ACRP30-adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073–85.
80. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty acid oxidation by activating AMP activated protein kinase. Nat Med 2002;8:1288–95.
81. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784–92.
82. Hopkins TA, Ouchi N, Shibata R, et al. Adiponectin actions in the cardiovascular system. Cardiovasc Res 2007;74:11–8.
83. Fesus G, Dubrovska G, Gorzelnaik K, et al. Adiponectin is a novel humoral vasodilator. Cardiovasc Res 2007;75:719–27.
84. Shibata R, Izumiya Y, Sato K, et al. Adiponectin protects against the development of systolic dysfunction following myocardial infarction. J Mol Cell Cardiol 2007;42:1065–74.
85. Yokota T, Oritani K, Takahashi I, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000;96:1723–32.
86. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697–703.
87. Cnop M, Havel PJ, Utzschneider KM, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity, and plasma lipoproteins: evidence of independent roles of age and sex. Diabetologia 2003;46:459–69.
88. Bruun JM, Lihn AS, Verdich C, et al. Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. Am J Physiol Endocrinol Metab 2003;285:E527–33.
89. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;114:1752–61.
90. Hong SD, Park CG, Seo HS, et al. Associations among plasma adiponectin, hypertension, left ventricular diastolic dysfunction, and left ventricular mass index. Blood Press 2004;13:236–42.
91. Brunson BL, Zhong Q, Clarke KJ, et al. Serum concentrations of adiponectin and characterization of adiponectin protein complexes in dogs. Am J Vet Res 2007;68:57–62.
92. Ishioka K, Omachi A, Sagawa M, et al. Canine adiponectin: cDNA structure, mRNA expression adipose tissues and reduced plasma levels in obesity. Res Vet Sci 2006;80:127–32.

93. Zini E, Linscheid P, Franchini M, et al. Partial sequencing and expression of genes involved in glucose metabolism in adipose tissues and skeletal muscle of healthy cats. Vet J 2009;80:66–70.
94. Lazar MA. Resistin and obesity associated metabolic diseases. Horm Metab Res 2007;39:710–6.
95. Komatsu T, Itoh F, Mikawa S, et al. Gene expression of resistin in adipose tissue and mammary gland of lactating and non-lactating cows. J Endocrinol 2003; 178:R1–5.
96. Dai MH, Xia T, Chen XD, et al. Cloning and characterization of porcine resistin gene. Domest Anim Endocrinol 2006;30:88–97.
97. Banerjee RR, Rangwala SM, Shapiro JS, et al. Regulation of fasted blood glucose by resistin. Science 2004;303:1195–8.
98. Steppan C, Bailey ST, Bath S, et al. The hormone resistin links obesity to diabetes. Nature 2001;409:307–12.
99. Steppan CM, Lazar MA. The current biology of resistin. J Intern Med 2004;255: 439–47.
100. Engeli S, Schling P, Gorzelniak K, et al. The adipose tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome. Int J Biochem Cell Biol 2003;35:807–25.
101. Rahmouni K, Mark AI, Haynes WG, et al. Adipose depot specific modulation of angiotensinogen gene expression in diet induced obesity. Am J Physiol Endocrinol Metab 2004;286:E891–5.
102. Henegar JR, Bigler SA, Henegar LK, et al. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 2001;12:1211–7.
103. Lee YH, Pratley RE. The evolving role of inflammation in obesity and the metabolic syndrome. Cuurr Diab Rep 2005;5:70–5.
104. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83:461S–5S.
105. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792–800.
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.
107. Hotamisligil GS, Shargill NS, Speigelman BM. Adipose expression of tumor necrosis factor alpha: direct role in obesity linked insulin resistance. Science 1993;259:87–91.
108. Moller DE. Potential role of TNF alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab 2000;11:212–7.
109. Hotamisligil GS. The role of TNF alpha and TNF receptors in obesity and insulin resistance. J Intern Med 2006;245:621–5.
110. Merlens I, Van Gaal LF. Visceral fat as a determinant of fibrinolysis and hemostasis. Semin Vasc Med 2005;5:48–55.
111. Veiga APM, Price CA, Oliveira ST, et al. Association of canine obesity with reduced serum levels of C-reactive protein. J Vet Diagn Invest 2008;20:224–8.
112. Kopelman PG. Obesity as a medical problem. Nature 2000;404:635–43.
113. Vega GL. Obesity and the metabolic syndrome. Minerva Endocrinol 2004;29: 47–54.
114. Trayhurn P, Beattie I. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 2001;60:329–39.
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,

golden retrievers, Labrador retrievers, and Rottweilers. J Am Vet Med Assoc 2001;219:1719–24.
116. Daminet S, Jeusette I, Duchateau L, et al. Evaluation of thyroid function in obese dogs and in dogs undergoing a weight loss protocol. J Vet med A Physiol Pathol Clin Med 2003;50:213–8.
117. Ferguson DC, Caffail Z, Hoenig M. Obesity increases free thyroxine proportionally to nonesterified fatty acid concentrations in adult neutered female cats. J Endocrinol 2007;194:267–73.
118. Pena C, Suarez L, Bautista I, et al. Relationship between analytic values and canine obesity. J Anim Physiol Anim Nutr 2008;92:324–5.
119. Stone RC, Berghoff N, Steiner JM, et al. Use of a bioelectric impedance device in obese and lean healthy dogs to estimate body fat percentage. Vet Ther 2009; 10:1–12.
120. Jordan E, Kley S, Le NA, et al. Dyslipidemia in obese cats. Domest Anim Endocrinol 2008;35:290–9.
121. Sin DD, Sutherland ER. Obesity and the lung: obesity and asthma. Thorax 2008; 63:1018–23.
122. Johnston RA, Theman TA, Lu FL, et al. Diet induced obesity causes innate airway hyperresponsiveness to methacholine and enhances ozone-induced pulmonary inflammation. J Appl Physiol 2008;104:1727–35.
123. Wren JA, Gossellin J, Sunderland SJ. Dirlotapide: a review of its properties and role in the management of obesity in dogs. J Vet Pharmacol Ther 2007;30(Suppl 1):11–6.
124. Wren JA, King VL, Campbell SL, et al. Biologic activity of dirlotapide, a novel microsomal triglyceride transfer protein inhibitor, for weight loss in obese dogs. J Vet Pharmacol Ther 2007;30(Suppl 1):33–42.