The Epidemic of Canine Obesity and its Role in Osteoarthritis

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ABSTRACT

The epidemic of obesity in dogs parallels the trend that is being observed in humans. Obesity is associated with many adverse conditions and impacts quality of life, as well as longevity. Adipose tissue is now recognized as a major endocrine organ. Obesity is currently accepted as a chronic inflammatory condition, resulting in several obesity-associated illnesses. This review article highlights the role of obesity in chronic systemic inflammation, and the major role of hormones, cytokines and other cell-signaling substances secreted by adipocytes (adipokines) in the development of osteoarthritis. The latter has been shown to be more important than obesity-associated body weight excess in rodents. The review also stresses the importance of body weight loss in treatment of osteoarthritis in dogs.

Keywords: Canine, obesity, osteoarthritis, white adipose tissue, leptin

INTRODUCTION

Canine obesity is the most common nutritional health problem in dogs (1, 2). Many similarities exist between obesity in dogs and humans (2-12). For example, the number of overweight or obese dogs has reached epidemic proportions, as in humans. In 1986, the prevalence of obesity in dogs in the United Kingdom was estimated to be approximately 24% (2). A similar study in Australia in 2005, has estimated that 41% of dogs were overweight or obese (3), and in the United States, it is estimated that 50% of dogs between 5 and 10 years and 55.6% of dogs of all ages are obese or overweight (4,13). Similar trends have occurred in humans. According to the United States Center for Disease Control and Prevention, in 1990 the prevalence of obesity was up to 15% (5). However, by 2010, its prevalence had reached over 20%, while in 36 states, its prevalence was above 25% and in 12 of these states the prevalence was above 30%. Approximately one-third of the adults in the USA (33.8%) are obese (5). Evidence shows that the prevalence of obesity in both dogs and humans is progressively and continuously increasing despite the promotion of physical activity and dietary and pharmacological attempts to control body weight (2, 3, 5, 13, 14).

Another similarity between obesity in humans and in dogs is the increase in diagnoses of obesity-related health problems. The World Health Organization has declared obesity to be the most important human health problem facing the Western World (6). Several health problems are caused or complicated by obesity in dogs, including chronic inflammation (7-9), osteoarthritis (OA) (10), pulmonary and cardiovascular disease (11), pancreatitis (12), and increased anesthesia-related morbidity (15). The latter occurs because various anesthetic drugs are fat–soluble, so recovery of obese dogs from anesthesia may be prolonged (15). In addition, obesity decreases both quality of life and life expectancy (10).

The understanding of the role of obesity in the development of several obesity-related health problems has changed dramatically over the last 15 years. Decreasing the number of chronic health problems facing dogs, as in humans, should thus also focus on decreasing the occurrence of obesity, which is an underlying cause of some of these conditions.

ADIPOSE TISSUE IS A MAJOR ENDOCRINE ORGAN

For many years, white adipose tissue (WAT) was considered mostly metabolically inert, and its primary role in disease was attributed to its effects of increased weight bearing, joint stress and cardiac workload. However, understanding of the physiologic role of WAT has changed since 1994, with the discovery of leptin, a hormone produced predominantly by WAT (16). Since then, several other hormones, cytokines and other cell-signaling substances, collectively referred to as adipokines, have been shown to be secreted by WAT (17, 18).

In obese rodents, adipose tissue shows inflammation and progressive macrophage infiltration, which can modify adipocyte paracrine function (19,20). In obese individuals, adipocytes secrete low levels of tumor necrosis factor-alpha (TNF-α), which stimulates preadipocytes to produce monocyte chemoattractant protein-1 (MCP-1). The latter attracts macrophages to the adipose tissue (19). Increased leptin secretion by adipocytes may also contribute to macrophage accumulation in the adipose tissue, by stimulating their transport to adipose tissue (21). Once these macrophages accumulate in the adipose tissue and become active, they, along with adipocytes, can perpetuate a vicious cycle of macrophage recruitment and production of inflammatory cytokines (20). These findings have led to the realization that adipose tissue should no longer be viewed as a simple vehicle for storage and release of fatty acids. Instead, adipose tissue is currently viewed as an important endocrine and signaling tissue, and adipokines extensively interact with other organs in the overall physiologic and metabolic control (22, 23).

LEPTIN

Leptin is a protein hormone (23, 24), secreted primarily by adipocytes that plays a key role in energy balance regulation, and its transcriptional regulation depends on energy flux within adipocytes (23-25). It is constitutively secreted by adipocytes and achieves its biologic effects by interacting with specific receptors (Ob-R) (26). Leptin stimulates energy expenditure (through thermogenesis), thereby assisting in balancing excessive caloric intake effects (27). Its release from adipose tissue is a key trigger in the hypothalamus, resulting in decreased appetite and food intake in normally responsive, non-obese individuals (16). The effects of leptin are not limited to thermogenesis. There is a wide pattern of the Ob-R expression in peripheral tissues (28), resulting in leptin's involvement in a wide variety of physiologic processes, including insulin secretion (29), reproductive functions (30), angiogenesis (31), immune functions (32) and bone metabolism (33,34).

In humans and rodents, plasma leptin concentrations are highly correlated with body mass index (BMI), and most obese individuals show high plasma leptin concentrations. One reason for this increase in leptin concentration in obese individuals is an increased amount of leptin-secreting adipose tissue (35). Furthermore, increased leptin levels induce leptin resistance in target cells and interfere with the normal hypothalamic feedback that down regulates food intake (36, 37). As a result, leptin becomes ineffective in controlling food intake, a condition known as leptin resistance (36, 37). A similar obesity-associated increase in plasma leptin concentration occurs in dogs and the greater the degree of obesity the higher the plasma leptin concentration (7-9). A study in dogs with different body condition scores (BCS) has shown that plasma leptin concentrations increase with an increase in BCS. Plasma leptin concentrations of 3.0 ± 0.4 ng/mL, 8.6 ± 0.7 ng/mL; and 12.8 ± 0.8 ng/mL were observed in dogs with BCSs of 3/5, 4/5 and 5/5, respectively. Therefore, plasma leptin concentration is a good index of adiposity in dogs, which is also true in humans and rodents (38).

Leptin also affects immune system cells' cytokine production, and leptin transcription is increased by proinflammatory cytokines, such as TNF-α, interleukin (IL)-1β, and IL-6 (39). Increased obesity-associated leptin secretion by adipocytes associated with obesity stimulates macrophage transport to the adipose tissue and production of inflammatory cytokines, contributing to the obesity-associated chronic inflammation (21). As a result, leptin appears to possess proinflammatory functions, and in addition, it may contribute to the generation of oxidative injury (40, 41).

Leptin is thought to regulate bone mass, although it is unclear whether its role is anti-osteogenic or anabolic in bone formation due to its functions in several alternate pathways (33,34). Peripheral leptin administration has been show to directly stimulate bone growth (42, 43). Conversely, central leptin administration indirectly involves a hypothalamic relay that leads to suppression of bone formation (44-46). This latter result is in agreement with the observation that obese humans who are resistant to leptin's central action are protected from osteoporosis (47). However, a more recent

study, conducted three-dimensional bone scans of 115 young women with normal (<32%) and high (>32%) body fat levels, and after adjusting for differences in muscle mass surrounding bones, the investigators concluded that the bones of the high body fat participants were 8 to 9 per-cent weaker compared to those of the normal body fat participants (48). Although the exact mechanism by which excess fat hinders bone strength is unclear, studies in obese rats showed that their bone marrow produces more fat cells but fewer bone cells (49). Because fat and bone cells are derived from a common precursor, it is possible that fat cell production may be favored over bone-cell production in obese people.

ADIPONECTIN AND HOW DOGS DIFFER

Adiponectin, known as adipoQ, apM1, Acrp30 and GBP28, is specifically and highly expressed in WAT (50, 51). It circulates as a low molecular weight (LMW) trimer, a medium molecular weight (MMW), hexamer (trimer-dimer) or as a large multimeric high molecular weight (HMW) isoform (52, 53). It plays an important role regulating energy homeostasis, increasing insulin sensitivity (54, 55), and has anti-inflammatory properties in humans and rodents (27,56,57). In non-obese individuals, insulin stimulates secretion of adiponectin by adipocytes. In turn, adiponectin suppresses hepatic glucose production (58) and increases hepatic and skeletal muscle fatty acid metabolism, thereby ameliorating insulin resistance (59, 60). In rodents, adiponectin also increases skeletal muscle glucose uptake (60). These effects of adiponectin on both liver and skeletal muscle, increase insulin sensitivity, lower blood glucose concentration, and decrease tissue triglyceride content (60). Adiponectin also suppresses macrophage TNF-α production, thereby exhibiting anti-inflammatory properties (61). In contrast, production of reactive oxygen species and proinflammatory cytokines, such TNF-α and IL-6, associated with increased adiposity, inhibit adiponectin gene expression (62, 63).

In contrast to leptin, increases in fat mass results in decreased circulating adiponectin concentrations, while weight loss leads to increases in its concentrations in humans (64), primates (65) and rodents (66). In humans, low levels of circulating total or HMW adiponectin concentrations are not only associated with insulin resistance, but predictive of progression to type-2 diabetes mellitus (DM) metabolic syndrome (67,68). However, recent studies have shown that adiponectin concentrations do not differ between obese and lean dogs (69-71). This lack of decrease in adiponectin concentration in obese dogs may explain why obese dogs do not develop type-2 DM, such as occurs in obese humans, in whom decreased adiponectin concentrations and DM occur.

Historically, adiponectin was thought to have primarily anti-inflammatory effects on joints. However, more recently, it is been shown to possess both anti- and pro-inflammatory effects (27, 72, 73). The anti-inflammatory effects of adiponectin are primarily related to its effects in decreasing TNF-α, IL-1β, and MMP-3 expression in synovial fibroblasts. The pro-inflammatory effects of adiponectin include induction of type II nitric oxide synthase (NOS2), IL-6, matrix metalloproteinases (MMP) -3 and -9, monocyte chemoattractant protein 1 (MCP-1) and prostaglandin E_2 in chondrocytes. As a result, adiponectin may actually contribute to cartilage destruction in OA in some species.

OBESITY AND OSTEOARTHRITIS

Obesity and OA both adversely affect health and quality of life in dogs. OA is estimated to affect as many as 20% of dogs above one year of age (74). According to market research statistics on pet ownership, published by the American Veterinary Medical Association in 2007, there are approximately 72 million dogs in the U.S. (75). Although it is unknown how many of these dogs are above one year of age, it is safe to assume that millions of dogs are adversely affected by OA annually.

Obesity and OA have been positively associated in humans. Obesity has been identified as a risk factor for development of knee and hand OA in humans, as well as for progression of the former (76-79). There is a growing body of evidence in humans suggesting that leptin has a detrimental effect on articular cartilage, and it plays a role in the pathogenesis of OA (80). Leptin also has an inhibitory effect on the long-term growth of cultured chondrocytes, and induces production of IL-1, MMP- 9 and -13 in a dose dependent manner indicating that leptin has a catabolic effect on chondrocyte metabolism (81).

A study in humans has evaluated synovial fluid leptin concentration in OA patients undergoing knee replacement surgery or knee arthroscopy (82). Samples from 14 men and 6 women showed synovial fluid leptin concentration of 8.16

+ 5.5 µg/L and 12.95 + 8.92 µg/L, respectively. The mean body mass index (BMI) in these men and women were 28.15 + 4.26 kg/m^2 and 26.04 + 4.03 kg/m^2, respectively, and synovial leptin concentrations were positively correlated with BMI (r = 0.572, P < 0.01). This significant correlation between BMI and synovial fluid leptin concentration suggests that this LMW circulating adipokine reaches the synovial fluid by diffusion through the synovial membrane and that it is overexpressed in the knee joint in humans with OA, especially in those individuals who are concurrently obese (82).

In that same study (82), forty nine biopsy specimens of tibial plateaus and osteophytes from the condyles were also collected from 11 patients during knee replacement surgery, and compared to normal knee joint cartilage obtained from two transplant donors. Results showed that there was a marked expression of leptin in OA cartilage, especially in fibrillated cartilage with clusters and in osteophytes, while few chondrocytes from normal cartilage produced leptin (82). The same study also showed that leptin has a stimulus effect on both proteoglycan synthesis and growth factor expression in rat cartilage, suggesting a new peripheral function of leptin as a key regulator of chondrocyte metabolism. The authors concluded that leptin may play an important role in the pathogenesis of OA by modulating chondrocyte functions and by contributing to osteophyte formation (82).

Another study in rodents evaluated leptin effects on eicosanoid synthesis in cultured rat alveolar and murine peritoneal macrophages. Leptin enhanced prostaglandin E2 and leukotriene synthesis in a dose-dependent manner (83). Leptin was also shown to enhance macrophage arachidonic acid (AA) release. The authors concluded that the increased occurrence of inflammatory obesity-associated diseases, such as OA, may be related to the ability of leptin to increase AA release and eicosanoid synthesis (83).

A recent study in mice has shown that leptin plays an important role in the development of OA in obese mice (84) The histopathological changes in the knee joints of leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice were compared to wild-type mice. Results showed that extreme obesity due to impaired leptin signaling induced alterations in subchondral bone morphology without increasing the proportion of knee OA. It was therefore concluded that increased body fat *per se* may not be a risk factor for knee joint degeneration, because in the absence of leptin signaling, systemic inflammation was insufficient to induce knee OA. These findings suggest that leptin concentration, which increases with increasing adiposity, plays a key role in the development of OA (84).

In dogs, there is a positive association between obesity and OA, although a clear cause and effect mechanism has not yet been proven. However, it seems likely that similar processes to those described in humans and rodents also occur in dogs. Results of a 13-year longitudinal life-span study, conducted by Nestle Purina, support the theory that obesity increases the prevalence of OA in dogs (85-88). In this study, 48 Labrador Retrievers of seven litters were sex- and body weight-matched in pairs and randomly and evenly divided into either a control-fed group or a restricted-fed group. The control-fed group was initially fed *ad libitum*, and at approximately three years of age, their intake was reduced to 62.1 kcal of metabolizable energy per kilogram of ideal body weight per day. The restricted-fed group was fed 75% of the food amount provided to the control-fed group. Mean (± SEM) BCS during the period from 6 to 12-years of age was significantly (P <0.01) higher in the control-fed group (6.7/9 ± 0.19) compared to the restricted fed group (4.6/9 ±0.19) (10). By eight years of age, the hip joints had the most severe OA lesions, and the occurrence of OA of the hip joints in the control-fed group (15/22) was significantly higher (P = 0.01) compared to the restricted-fed group (3/21) (86). In addition, OA affecting multiple joints was significantly (P = 0.01) more common in the control-fed group compared to the restricted-fed group. The need for treatment of OA was also delayed in the restricted-fed group compared to the control-fed group (86). It is important to keep in mind that the control-fed dogs were not defined as obese, but rather were only overweight, with a mean BCS of 6.7/9 (SD 0.19) (86). Had the dogs in the control-fed group had a BCS of 8/9 or 9/9, like some client-owned dogs, the difference in the results between the two groups might have even been more dramatic. Nonetheless, this study is important because it documented that overweight not only increased the occurrence of OA in dogs, but it also increased its severity.

WEIGHT LOSS IN MANAGEMENT OF OSTEOARTHRITIS

In humans, strong evidence supports weight loss as a therapeutic intervention in obese individuals with OA. One study showed that a mild, 5.1% reduction in body weight signifi-

cantly decreased the self-reported disability in obese humans with knee OA (89).

There is also good evidence supporting weight loss as a therapeutic intervention in obese dogs with OA. A study of 16 overweight and obese dogs (BCS 6-8/9) with OA of the hips that were evaluated using kinetic gait analysis showed that weight loss that normalized the BCS to 4-5/9 resulted in significant improvement in kinetic gait analysis results when compared to baseline results (90). This study has documented objective improvement in OA-associated lameness in overweight and obese dogs when they lost weight (90). Another clinical study evaluated nine overweight dogs with OA-associated lameness (91). Subjective lameness scores, using a numerical score and a visual analogue scale, showed that a 6.2% body weight reduction significantly improved subjective lameness scores (91)

A prospective clinical trial has evaluated 29 dogs with lameness and OA of a single joint (92). These dogs had BCSs of 4-5/5. Subjective lameness and pain scores, as well as objective kinetic gait analysis, were recorded before and after weight loss. In this study, weight loss was combined with either intense physiotherapy or moderate physiotherapy. The dogs in the intense physiotherapy and weight loss group showed a greater improvement in lameness compared to those in the moderate physiotherapy-weight loss group. Although the study design does not allow assessment of the individual roles of weight loss and intensity of physiotherapy in the improvement of lameness, it did show that their combination did decrease disability in dogs with OA (92).

In a recent clinical study, 14 obese client-owned dogs with clinical and radiographic signs of OA of the hip and/or elbow were subjectively and objectively evaluated prior to, and after weight loss, which was the only therapy provided for OA (93). Weight loss decreased the subjectively assessed clinical signs of lameness, and significant effects were seen with as little as loss of 6.10% of body weight. Objective kinetic gait analysis results in obese dogs with elbow OA and forelimb lameness improved with weight loss of 8.85% body weight (93). Therefore, even moderate weight loss potentially results in significant improvement of OA-associated clinical signs in obese dogs, and weight loss should be considered an important component of both short- and long-term management of such dogs.

CONCLUSIONS

Obesity is becoming increasingly more common in dogs despite many attempts to control body weight with energy-restricted diets, increased exercise and use of drugs. The understanding of the role obesity plays in OA and other health problems is progressively increasing. The association of obesity with chronic inflammation, which plays a major role in the development of certain associated conditions, such as OA, is now recognized. Therefore managing obesity is a key factor to decreasing the occurrence of certain obesity-associated diseases, such as OA, and the associated treatment cost of such conditions.

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