Obesity, its associated disorders and the role of inflammatory adipokines in companion animals

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Abstract
Obesity is characterised by an expansion of white adipose tissue mass that can lead to adverse health effects, such as decreased longevity, diabetes mellitus, orthopaedic and respiratory disease and neoplasia. Once thought a passive fuel depot, adipose tissue is now recognised as an active endocrine organ that communicates with the brain and peripheral tissues by secreting a wide range of hormones and protein factors, collectively termed adipokines. Examples include leptin, adiponectin, cytokines (tumour necrosis factor-α, interleukin-6), chemokines, acute phase proteins, haemostatic and haemodynamic factors and neurotrophins. Adipokines can influence various body systems, and perturbation of normal endocrine function is thought central to the development of many associated conditions. This review focuses on the medical consequences of obesity in companion animals, assesses the endocrine function of adipose tissue in disease pathogenesis, and highlights the potential role of adipokines as biomarkers of obesity-associated disease.

Introduction
Obesity occurs where the accumulation of excess body fat adversely affects health (Kopelman, 2000). Recent figures have indicated that approximately 25% of men and women in the United Kingdom are obese (body mass index [BMI] > 30), which represents a threefold increase in prevalence since 1980 (Rennie and Jebb, 2005). Obese humans are at higher risk of developing a number of diseases including type II diabetes mellitus, hypertension, coronary heart disease, certain cancers (e.g. breast, ovarian, prostate), osteoarthritis, respiratory disease, and reproductive disorders (Kopelman, 2000).

As with humans, overweight and obesity is a major concern in the companion animal population. In three of the most recently published canine studies, 29–34% of dogs were classed as overweight and 5–8% were judged obese (Lund et al., 2006), and in cats the latest data indicate that 19–29% and 6–8% of animals are overweight and obese, respectively (Lund et al., 2005). The prevalence of obesity in the pet population also appears to be increasing, given that previous reports suggested prevalences of 24% in dogs (Edney and Smith, 1986) and 6–12% in cats (Anderson, 1973). Similar to humans, obesity also has detrimental health effects in dogs and cats (German, 2006), and is now recognised as a major disease in companion animal medicine. This review highlights the medical consequences of obesity in pets and examines the potential endocrine function of adipose tissue in disease pathogenesis.

The pathological consequences of obesity

A recent study of cause-specific mortality in 900,000 humans, revealed BMI to be a strong predictor of overall mortality (Prospective Studies Collaboration, 2009). Relative to the apparent optimum BMI of 22.5–25 kg/m², median lifespan is reduced by 2–4 years and 8–10 years, at BMIs of 30–35 kg/m² and 40–45 kg/m², respectively. Obese humans are more likely to suffer from diseases such as the metabolic syndrome, type II diabetes mellitus, hypertension, coronary heart disease, certain cancers, osteoarthritis, respiratory and liver disease (Table 1). Obesity is also known to have detrimental effects on both the health and longevity of dogs and cats.

A long-term colony-based research study, comparing life-long ad libitum feeding with energy restriction (where animals were fed approximately 75% of the ad libitum ration), demonstrated that ad libitum-fed dogs tended to be overweight, had a shorter lifespan and had increased risk of associated disease (Kealy et al., 2002). Obesity is also reported to be a major risk factor for orthopaedic disease, diabetes mellitus, respiratory and urinary tract disease (Table 1).
Endocrine function of white adipose tissue

Although once considered a passive fuel depot, white adipose tissue (WAT) is now recognised as an active endocrine organ that communicates with the brain and peripheral tissues by secreting a wide range of hormones and protein factors, collectively termed adipokines (Trayhurn, 2005). This term is restricted to the proteins secreted by adipocytes themselves and not by WAT as a whole, so as to exclude proteins secreted by other cells found in WAT such as macrophages (Trayhurn and Wood, 2004).

Some 100 different adipokines have been characterised in humans and rodents, and this ‘adipokinome’ together with lipid moieties released by the adipocyte, constitute the ‘secretome’ of the fat cell (Fig. 1). The effects of these adipokines can influence many biological systems including glucose homeostasis, inflammation and immunity, haemostasis, fluid balance, vascular biology, haematopoiesis, cell proliferation, angiogenesis and neurotrophic functions (Radin et al., 2009). Although information is more limited, gene expression and protein secretion for a variety of adipokines have been documented from WAT of cats and dogs (Eisele et al., 2005; German et al., 2009a; Radin et al., 2009; Ryan et al., 2008, 2009).

Obesity as an inflammatory state

Obesity is characterised by chronic, low-grade systemic inflammation (Trayhurn, 2005). Levels of the inflammatory markers C-reactive protein (CRP), interleukin (IL)-6 and tumour necrosis factor alpha (TNF-α), are systemically raised in obese humans, whilst weight loss generally reverses this trend and can improve insulin sensitivity (Mancó et al., 2007). Since both pro-inflammatory cytokines and acute phase proteins (APPs) are produced by WAT, this tissue is thought to be an important source of the raised concentrations of these compounds in obese individuals and provides a link between obesity, insulin resistance and the metabolic syndrome (Trayhurn, 2005).

Tissue hypoxia

It has been proposed that expansion of WAT in obesity leads to decreased tissue perfusion (Trayhurn and Wood, 2004), leading to the recruitment of hypoxia inducible factor-1α (HIF-1α) transcription factor (Wood et al., 2007), which in turn triggers the production and release of inflammatory adipokines. The induction of HIF-1α can lead to decreased adiponectin production and increased expression of leptin, macrophage inhibitory factor (MIF), vascular endothelial growth factor (VEGF) and plasminogen activator inhibitor (PAI-1) (Chen et al., 2006).

Table 1

Diseases associated with overweight and obesity in humans, dogs and cats (Kopelman, 2000; German, 2006).

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine and lipid metabolism</td>
<td>Type 2 diabetes, metabolic syndrome, dyslipidaemias</td>
</tr>
<tr>
<td>Human</td>
<td>Hypothyroidism, hyperadrenocorticism, diabetes mellitus, insulin resistance, metabolic syndrome (experimental)</td>
</tr>
<tr>
<td>Dog</td>
<td>Diabetes mellitus, hepatic lipodisosis</td>
</tr>
<tr>
<td>Cardio-respiratory</td>
<td>Coronary heart disease, atherosclerosis, hypertension, obstructive sleep apnoea, asthma</td>
</tr>
<tr>
<td>Human</td>
<td>Tracheal collapse, expiratory airway dysfunction (experimental), hypertension (of doubtful clinical significance), portal vein thrombosis, myocardial hypoxia</td>
</tr>
<tr>
<td>Dog</td>
<td>Lameness</td>
</tr>
<tr>
<td>Orthopaedic (impaired mobility)</td>
<td>Osteoarthritus, musculoskeletal pain, gout</td>
</tr>
<tr>
<td>Human</td>
<td>Osteoarthritus, cruciate ligament disease, humeral condylar fractures, intervertebral disc disease, hip dysplasia</td>
</tr>
<tr>
<td>Dog</td>
<td>Lameness</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Various cancers including: breast (post-menopausal), renal, endometrial, prostatic, oesophageal, colorectal, hepatocellular (Diabetic) nephropathy</td>
</tr>
<tr>
<td>Human</td>
<td>Transitional cell carcinoma, mammary carcinoma (some studies)</td>
</tr>
<tr>
<td>Dog</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Urogenital</td>
<td>Urinary tract disease, Calcium oxalate urolithiasis, transitional cell carcinoma; glomerular disease (experimental); dystocia</td>
</tr>
<tr>
<td>Human</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Dog</td>
<td>Increased risk of urinary tract disease</td>
</tr>
<tr>
<td>Alimentary</td>
<td>Pancreatitis, hepatic steatosis, cirrhosis</td>
</tr>
<tr>
<td>Human</td>
<td>Immune function</td>
</tr>
<tr>
<td>Dog</td>
<td>Increased oral cavity and gastrointestinal disease</td>
</tr>
<tr>
<td>Other</td>
<td>Depression, post-operative complications, dermatological disease</td>
</tr>
</tbody>
</table>
Adipokines and cancer

Studies in rodents and humans have also linked obesity to an increase in the production of reactive oxygen species within WAT, leading to oxidative stress and elevated production of pro-inflammatory markers (Furukawa et al., 2004). Increased endoplasmic reticulum stress has also been described, with similar pathological consequences (Hotamisligil, 2005).

Adipose tissue macrophages

Macrophages are an important component of WAT, and accumulate during obesity (Weisberg et al., 2003). Since WAT macrophages are derived from bone marrow, expansion during obesity is related to recruitment of circulating monocytes, likely due to increased expression of macrophage chemotactic factor (MCP-1) and MIF by WAT (Weisberg et al., 2003). Increased macrophage numbers can then result in a significant amplification of inflammatory pathways within adipose tissue, involving extensive cross-talk between macrophages and adipocytes (Trayhurn, 2005). Macrophage-conditioned media can up-regulate various genes associated with inflammation in adipocytes including many matrix metalloproteinase genes, suggesting that macrophages can stimulate tissue remodelling during adipose tissue expansion in obesity (O’Hara et al., 2009). Obesity is also thought to induce a phenotypic switch in macrophages within adipose tissue from an M2, or ‘alternatively activated’, state in lean individuals to an M1, or ‘classically activated’, state in the obese. Such M1 macrophages are capable of increasing gene expression of pro-inflammatory cytokines such as TNF-α (Lumeng et al., 2007).

Adipokines and the development of obesity-associated disorders

There are two main mechanisms by which excessive WAT can predispose to disease. Firstly, the deposition of excess fat can have mechanical/physical effects that exacerbate orthopaedic disease, constrict upper airways, restrict grooming and reduce heat dissipation. Secondly, and most importantly, the perturbation of the normal endocrine function of WAT can trigger or exacerbate a number of associated conditions.

Obesity-related changes in adipokine profiles

In humans, the tissue expression and circulating concentration of many adipokines increase with increasing adiposity, as is the case for leptin (Considine et al., 1996), TNF-α (Hotamisligil et al., 1995), IL-6 and IL-18 (Esposito et al., 2003), serum amyloid A (SAA) (O’Brien et al., 2004), CRP (Esposito et al., 2003; O’Brien et al., 2004), haptoglobin (Chellini et al., 2004), angiotensinogen (Engeli et al., 2005), PAI-1 (Folsom et al., 1993), MIF (Church et al., 2005), and MCP-1 (Christiansen et al., 2005). An exception is adiponectin, the concentration of which is inversely related to bodyweight, and reduced WAT expression of this compound occurs in both obesity and type II diabetes mellitus (Abbasi et al., 2004).

Similar findings have been noted in companion animals, whereby increasing adiposity is related to increased plasma leptin concentration (Appleton et al., 2000; Sagawa et al., 2002) and decreased plasma adiponectin concentration (Ishioaki et al., 2006; Hoening et al., 2007). Furthermore, weight loss results in decreased leptin concentrations (Hoening et al., 2007; Jeuette et al., 2007), whilst the adiponectin concentration is increased (Ishioaki et al., 2006). Detectable circulating TNF-α concentrations are found in almost 50% of dogs with naturally occurring obesity, with concentrations declining significantly after weight loss (German et al., 2009b). The concentrations of CRP and haptoglobin were also found to be in the high-normal to mildly elevated range in obese dogs, with both parameters decreasing modestly after weight loss (German et al., 2009b).

Adipokines, the metabolic syndrome and insulin resistance

Insulin resistance is associated with obesity in various species including humans, dogs and cats (Kopelman, 2000; Hoening et al., 2007; German et al., 2009b). Furthermore, circulating levels of several adipokines are raised in both human type II diabetes and obesity. The most studied is TNF-α, which can promote insulin resistance at various levels, both centrally in the hypothalamus and within the adipocyte (Hotamisligil et al., 1994, 1995). Both decreased insulin sensitivity and elevated circulating TNF-α concentrations are found in obese dogs, suggesting a relationship also exists between these events in this species (German et al., 2009b). The management of obesity improves insulin sensitivity in humans (Hotamisligil et al., 1995), cats (Hoening et al., 2007) and dogs (German et al., 2009b). Plasma IL-6 concentrations are elevated in obese humans (Mohamed-Ali et al., 2001), and this cytokine is thought to play a direct role in insulin resistance by altering insulin signalling in hepatocytes (Senn et al., 2002). Elevated levels of PAI-1 have been linked to insulin resistance (Juhán-Vague et al., 1991), whilst circulating nerve growth factor (NGF) concentrations are increased in obesity and the metabolic syndrome in women (Bullo et al., 2005).

Leptin enhances the action of insulin on both the inhibition of hepatic glucose production and in stimulating glucose uptake (Barzili et al., 1997), perhaps explaining why leptin may have a role in the regulation of insulin sensitivity (Ebihara et al., 2001). Plasma leptin concentrations are independently associated with insulin sensitivity in both lean and overweight cats (Appleton et al., 2002). In addition, adiponectin acts as an insulin sensitisier by increasing fatty-acid oxidation, which in turn reduces the triglyceride content of these tissues in obese and type II diabetic mice (Yamauchi et al., 2001). There are also inverse correlations between plasma adiponectin concentration and risk factors associated with cardiovascular disease, such as impaired vasoreactivity and levels of CRP (Ouchi et al., 2003).

Adipokines and inflammation

Obesity is characterised by chronic, low-grade systemic inflammation, with increased concentrations of inflammatory markers such as CRP, IL-6 and TNF-α (Trayhurn and Wood, 2004). The concentrations of IL-1β is increased in obese humans (Um et al., 2004), with the combination of elevated IL-1β and IL-6 increasing the risk of both type II diabetes and the metabolic syndrome (Spranger et al., 2003). Plasma IL-18 concentration is also elevated in obesity and the level of this cytokine declines in response to weight loss (Esposito et al., 2002). Increased serum IL-18 concentration has been associated with hypoadiponectinaemia in obesity independent of insulin resistance (Straczkowski et al., 2007). The expression of IL-10 is raised in obesity (Juge-Aubry et al., 2005) and, in contrast to most other cytokines secreted by WAT, IL-10 is thought to play an anti-inflammatory role countering pro-inflammatory agents such as lipopolysaccharide (LPS) and TNF-α.

In addition to the effects of APPs and pro-inflammatory cytokines, leptin is a significant modulator of both immune and inflammatory responses, including the activation of neutrophils, macrophages and natural killer cells and in influencing lymphocyte proliferation (Otero et al., 2003). Adiponectin has also a strong anti-inflammatory function (Tilg and Wolf, 2005), and the hypoadiponectinaemia seen in obesity has been associated with the raised levels of several pro-inflammatory cytokines such as IL-6,
IL-8 and TNF-α (Engeli et al., 2003). It has been suggested that the raised levels of these endogenous cytokines may be directly responsible for the inhibition of adiponectin secretion (Bruun et al., 2001).

**Adipokines, hypertension and thrombosis**

Elevated angiotensinogen in obese humans is associated with the development of hypertension (Engeli et al., 2003). The expression of WAT angiotensinogen decreases in response to weight loss in humans, and is thought to contribute to the fall in blood pressure observed (Engeli et al., 2005). Although hypertension occurs in obese dogs, it is mild and of doubtful clinical significance (Bodey and Mitchell, 1996). It remains unclear if this species difference is the result of differences in the pattern of adipokine expression. Plasminogen activator inhibitor (PAI)-1 production is increased in human obesity, is linked to several pro-inflammatory cytokines, including TNF-α (Wang et al., 2005) and IL-6, and has also been associated with increased risk of the atherosclerotic complications associated with obesity (Ziccardi et al., 2002). This provides evidence of a strong link between visceral adiposity, PAI-1 levels and the increased incidence of atherothrombosis frequently associated with human obesity.

**Adipokines and respiratory disease**

Human obesity is associated with both obstructive sleep apnoea and asthma, and the association can be partly explained by the physical impairment caused by fat on both chest wall and diaphragmatic function (Kopelman, 2000). However, a large waist (a marker of visceral adiposity) is also associated with an increased prevalence of asthma in women of normal bodyweight. Since visceral adipose tissue is more metabolically active than subcutaneous fat, it is tempting to speculate that endocrine factors may also play a role. Indeed, many of the pro-inflammatory factors increased in the plasma of obese subjects are also central to the pathogenesis of asthma (Chung and Barnes, 1999). For instance, IL-6 can modulate T-helper 2 (Th2) cell immunity (Heijink et al., 2002), TNF-α can augment airway inflammation (Thomas, 2001) and increases airway contractility (Sukkar et al., 2001), whilst leptin may facilitate airway hyper-responsiveness (Shore, 2007). However, in a recent study, although markers of systemic inflammation increased with obesity and Th2 cytokines were increased in asthma, a direct interaction between the two could not be demonstrated (Sutherland et al., 2008).

**Adipokines and orthopaedic disease**

Most of the increased risk for orthopaedic diseases, such as osteoarthritis (OA), can be explained by the ‘mechanical overload’ effect of obesity. However, the development of OA in non-weight-bearing joints, such as the hand, is also associated with increasing BMI in humans (Cicuttini et al., 1996), and symptomatic improvement of OA is more closely related to loss of body fat than overall BMI in humans (Cicuttini et al., 1996). In contrast, adiponectin can reduce adhesion molecule expression, providing some protection against carcinogenesis by inhibiting cancer cell growth and tumour-associated angiogenesis (Barb et al., 2007). Low adiponectin levels are observed in humans with various types of cancer, and might contribute to their incidence and severity (Barb et al., 2007).

Another potential link between obesity and cancer is hyperinsulinaemia, which can arise from the deranged adipokine expression associated with obesity, and has been directly associated with colon cancer in obese humans (Schoen et al., 1999). The inflammatory adipokines associated with obesity may also contribute to the development of pancreatic cancer by causing chronic inflammation, which may progress ultimately to pancreatic adenocarcinoma (Calle and Kaaks, 2004). Barrett’s oesophagus is a chronic oesophagitis, predominantly the result of chronic acid reflux commonly found in obese humans. This inflammation may be accentuated by chronic adipokine injury from peri-oesophageal adiposity, thereby enhancing the progression to high-grade dysplasia and ultimately to malignant neoplasia.

**Adipokines as potential biomarkers in companion animal obesity**

Given the plethora of endocrine factors associated with obesity, there is huge potential for these compounds to be used as biomarkers. However, given that the diagnosis of companion animal obesity is usually straightforward, there is little need to develop biomarkers as a diagnostic test. Of greater importance however would be the development of biomarkers to identify co-morbidities. Furthermore, alterations in such biomarkers may be helpful in monitoring the patient response to obesity management, not only directed at weight loss, but also at decreasing the risk of metabolic disease.

To date, the most promising biomarkers include plasma insulin (as a means of indirectly assessing insulin sensitivity) and circulating adipokines, particularly those of the inflammatory group. With respect to the latter, validated canine and feline commercial assays are already available for a number of these adipokines and their potential has been demonstrated in a recent canine study. The concurrence of insulin resistance and alterations in TNF-α, CRP and haptoglobin in obese dogs, found in this study, was similar to the sub-clinical state found in obese humans (German et al., 2009b). Moreover, significant decreases were noted after weight loss highlighting that these factors could be useful independent markers of response to therapy. Other potential adipokine biomarkers include leptin and adiponectin although validated, commercially available assays for these adipokines in companion animals have yet to be developed.

**Conclusions**

Adipose tissue has the capacity to secrete a wide range of endocrinologically active adipokines and perturbation of this func-
tion is thought central to the development of many conditions associated with obesity. Further work is required to establish if these compounds can be used as biomarkers to predict obesity-associated disease in companion animals.

Conflict of interest statement

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