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Oxidative Stress in Obesity: How Important Is It?

Korinn Saker, MS, DVM, PhD, DACVN
Department of Molecular and Biosciences
North Carolina State University
College of Veterinary Medicine
Raleigh, NC 27606
E-mail: Korinn_Saker@ncsu.edu

Introduction

This proceedings paper entertains the question of "How relevant is oxidative stress in obesity?" It defines oxidative stress and obesity, and then presents evidence to support a relationship between the two and the proposed relevance of this relation. This overview highlights chronological studies of significance (epidemiological to molecular) that encompass relevant population numbers and foci that help to conceptualize the understanding of the oxidative stress-obesity relationship first recognized in humans. The relevance of this relation has been subsequently emerging in veterinary medicine.

Glossary of Abbreviations
BCS: Body Condition Score
BMI: Body Mass Index
DM: Diabetes Mellitus
IBW: Ideal Body Weight
ROS: Reactive Oxygen Species
RS: Reactive Species
SAT: Subcutaneous Adipose Tissue
VAT: Visceral Adipose Tissue
VE: Vitamin E
WHR: Waist-to-Hip Ratio

Defining Oxidative Stress

The literature overflows with studies involving interest in oxidative stress. Commonly, oxidative stress is referred to as various pathologic changes seen in living organisms in response to excessive levels of cytotoxic oxidants and free radicals in the environment; an imbalance of the prooxidant antioxidant ratio in which too few antioxidants are produced or ingested or too many oxidizing agents are produced; an abnormal level of reactive oxygen species (ROS), such as free radicals (e.g., hydroxyl, nitric acid, superoxide) or non-radicals (e.g., hydrogen peroxide, lipid peroxide) that lead to damage (called oxidative damage) to specific molecules with consequential injury to cells or tissue.

Increased production of ROS occurs as a result of fungal or viral infection, inflammation, aging, ultraviolet radiation, pollution, excessive alcohol consumption, cigarette smoking, etc. and physiological stress on the body caused by the cumulative damage done by free radicals inadequately neutralized by antioxidants associated with aging. Chemists and biologists typically define oxidative stress as an imbalance in biological cells, in particular, between the state of two chemical processes: the formation of ROS, more generally reactive species (RS),[1] some of which qualify as oxygen free radicals, potent oxidizing (electron-capturing) atoms, ions or molecules; and the elimination or reduction of those oxidizing agents by antioxidants (reducing or electron-donating) atoms, ions or molecules.

Oxidative stress, therefore, may result from diminished antioxidant defense, excessive production of reactive oxygen species or a combination of both. The concept of oxidative stress occupies central importance in biology, as it applies, depending on circumstances, either to physiological phenomena essential for optimal functioning of organisms or to pathophysiological phenomenon, such as cardiovascular diseases, cancer and other clinical disease states, as well as to considerations of the mechanisms underlying aging.[2] Although it may be implied in other clinical disease states, in none of these more common perceptions of oxidative stress is the association of obesity actually highlighted.

There appears to be a more simplistic definition of obesity. It is commonly defined as the accumulation of excess body fat to the extent that it may have an adverse effect on health. Obesity is universally considered a medical condition. An objective measure of obesity in humans is reported as body mass index (BMI)>30 kg/m^2, with subcategories indicating the stage of obesity (i.e., Grades I to IV). Percentage (%) in excess of ideal body weight (IBW) and kilograms (kg) overweight are additional criteria used to define obesity. For example, an individual who is defined as morbidly (severe) obese would be >200% of their IBW and >40 kg overweight.[3] Obesity is defined in a quantitative fashion in veterinary patients as well, utilizing the practice of assigning a body condition score (BCS) to the animal. The dog or cat with a normal or ideal BCS would have approximately 20% body fat, whereas an animal defined as obese, very obese or extremely obese would have estimated body fat of 40, 50 and >60%, respectively.[4]

Before tackling whether oxidative stress in obesity

is relevant, it is paramount to establish a relationship between oxidative stress and obesity and what it constitutes.

Relations of Oxidative Stress and Obesity

A review of the literature documents the link between oxidative stress and the obese state. The predominance of these studies are human and rodent-model focused; several provide specific companion animal data. Examples of more recent studies provide evidence of altered oxidative biomarkers in conjunction with body fat mass conditions, along with associative changes in adipocyte function in the obese versus non-obese and the influence of weight loss.

Oxidant-antioxidant status was investigated in a group of severely obese prepubertal children in comparison with healthy subjects, and then followed through a dietary restriction weight-loss program.[5] All children underwent anthropometric measurements and determination of lipid profile, lag phase, malondialdehyde (MDA) and vitamin E concentration. Compared with controls, obese children had a significantly higher BMI (28.97±2.42 vs. 16.03±1.88 kg/m2; P=0.0002) and waist-to-hip ratio (WHR) (0.89±0.03 vs. 0.80±0.01; P=0.0004), and vitamin E levels were significantly decreased (21.12±14.96 vs. 35.54±13.62 µmol/liter; P=0.02). Conversely, MDA was significantly increased (0.90±0.31 vs. 0.45±0.24 nmol/mg; P=0.001). Both lag phase and MDA significantly correlated with BMI (r=-0.34 (P=0.004); r=0.57 (P=0.002). Interestingly, the oxidant status normalized after six months of dietary restriction (MDA, 0.47±0.09 nmol/mg; P=0.003), which was associated with a reduction of BMI (27.34±1.87 kg/m2; P=0.003), WHR (0.87±0.02; P=0.001) and fat mass (34.49± 2.68%; P=0.008), but returned to baseline levels together with body fat indices after another six months of free diet. Based on these study results, investigators concluded that altered oxidant-antioxidant status is present in severely obese children and is reversible with a dietary restriction weight-loss program.

Along this same vein, the suppressive effect of dietary restriction and weight loss in the obese on the generation of ROS by leukocytes, lipid peroxidation and protein carbonylation during both long- (4 weeks) and short-term (48 hour) dietary restriction has been reported.[6,7] Macronutrient restrictions lead to a 50% reduction in ROS generation by leucocytes and adiminution in the expression of NADPH oxidase, the enzyme that converts molecular oxygen to the superoxide radical. This reactive radical activates the redox sensitive proinflammatory transcription factor, NF-kB, which subsequently activates the transcription of most proinflammatory genes. These data imply that the prooxidant and proinflammatory effects of excessive macronutrient intake observed in the non-obese subjects are similar to those found in the obese in their basal fasting state, and that dietary restriction in the obese can indeed reduce proxidant biomarkers and their influence on the production of inflammatory proteins.

The 2007 Framingham Heart Study examined the relations of abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) to circulating inflammatory and oxidative stress biomarkers in 1,250 participants (52% women; age 60+/-9 years).[8] Biomarkers were examined in relation to increments of SAT and VAT after adjustment for age, sex, smoking, physical activity, menopause, hormone replacement therapy, alcohol, and aspirin use; additional models included body mass index and waist circumference. SAT and VAT were positively and similarly (with respect to strength of association) related to C-reactive protein, fibrinogen, intercellular adhesion molecule-1, interleukin-6, P-selectin, and tumor necrosis factor receptor-2. VAT was highly associated with urinary isoprostanes and monocyte chemoattractant protein-1 (R^2=0.10, P=0.002; R^2=0.08, P=0.04). The addition of body mass index and waist circumference identified a positive association of VAT with isoprostanes (P=0.0002) and monocyte chemoattractant protein-1 (P=0.008). These data support an association between both SAT and VAT with oxidative stress and inflammation.

A recent study evaluated the regulation of biomarkers of oxidative stress by the antioxidant, vitamin E (VE), in the obese and non-obese.[9] Three groups of Sprague–Dawley rats — control group fed normal chow; diet-induced obesity (DIO) group fed a high-fat diet; and intervention group fed a high-fat diet supplemented with VE (350 mg/kg) — were followed for 10 weeks. Serum levels of 8-epi-prostglandin-F2α correlated positively with body fat mass (r=0.61, P<0.05). Adiponectin and leptin levels were lower in the DIO group than in the control group, and VE intervention increased the expression of both leptin and adiponectin (P<0.05). Administration of an antioxidant decreased adipose tissue-associated hormone expression in the obese suggesting that antioxidants and, subsequently, a prooxidative state play an important role in obesity-related diseases.

Lee et al. reported a relationship between a specific endogenous antioxidant, glutathione peroxidase 3 (GPx3), and obesity.[10] They observed that GPx3 expression was reduced selectively in the adipose tissue of several obese animal models as decreasing plasma GPx3 level and that adipose GPx3 expression was greatly suppressed by prooxidative conditions such as high levels of TNF and hypoxia. In contrast, the antioxidant N-acetyl cysteine and the anti-diabetic drug rosiglitazone increased adipose GPx3 expression in obese and diabetic db/db mice. Addi-

tionally, they showed that GPx3 overexpression in adipocytes improved high glucose-induced insulin resistance and attenuated inflammatory gene expression whereas GPx3 neutralization in adipocytes promoted expression of proinflammatory genes. Taken together, their data suggest that suppression of GPx3 expression in the adipose tissue of obese subjects might constitute a vicious cycle to expand local reactive oxygen species accumulation in adipose tissue potentially into systemic oxidative stress and obesity-related metabolic complications.

Clearly, there is compelling evidence that one of the main clinical manifestations in obesity is increased systemic oxidative stress. In addition to the obese state, oxidative stress has been implicated in several forms of tissue damage and leads to pathological conditions such as irradiation damage, ischemia reperfusion injury and neurodegenerative diseases. Accumulated evidence also indicates that increased oxidative stress is strongly associated with metabolic disorders, which are often observed in obesity and morbid obesity. Dandona et al. pieced together numerous years of related studies to present the conceptual complex relations among obesity, inflammation, oxidative stress and metabolic states associated to insulin resistance (Figure 1)[11]; this introduced the potential link between oxidative stress and diabetes. Subsequently, others have corroborated that oxidative stress impairs insulin secretion by pancreatic β-cells,[12] as well as glucose transport into the muscle[13] and adipose tissue.[14] As expected, these adverse consequences of oxidative stress are magnified in the obese, and dysregulation of adipocytokine gene expression recently has been identified as an underlying factor.

In support of the role for adipocytokine gene expression in obesity and oxidative stress, there is much evidence indicating that adipose tissue is a metabolically active endocrine organ with cytokine and hormone involvement. Numerous adipoctye-derived proteins with endocrine function have been identified; those that have been more extensively researched include leptin, TNF-α, IL-6, MCP-1, PAI-1 and adiponectin. Leptin plays a key role in regulating energy intake and energy expenditure. It is secreted in direct proportion to adipose tissue mass, as well as nutritional status, and has been shown to alter cytokine production by immune cells and stimulate endothelial cell growth, angiogensis and wound healing. Adiponectin is exclusively secreted from adipose tissue and affects glucose flux and lipid catabolism. An inverse relationship between adiponectin and both insulin resistance and inflammatory states has been well documented. Adiponectin levels decline at the onset of obesity and insulin resistance. Additionally, this hormone has been shown to protect endothelial cells, a function thought to benefit prevention of atherosclerotic formation. Deficiency of adiponectin is reported to be an independent risk factor for developing metabolic syndrome and possibly diabetes mellitus (DM).

The proposed pathogenesis of metabolic syndrome as it relates to adipocyte-associated inflammation[15] is summarized in Figure 2. Cytokines, TNF-α, TNF-αR and IL-6 are expressed in adipose tissue of numerous species and have pronounced inflammatory actions. TNF is secreted mainly in proportion to the amount of subcutaneous fat stores and is positively correlated with inflammation and subsequent insulin resistance. Interleukin-6 acts as both a pro-inflammatory and anti-inflammatory cytokine. Secreted by T cells and macrophages, as well as adipose tissue, it stimulates the immune response to trauma or inflammation. In the healthy individual, systemic IL-6 concentrations increase with adiposity, with as much as one-third of the total circulating IL-6 originating from adipose tissue.

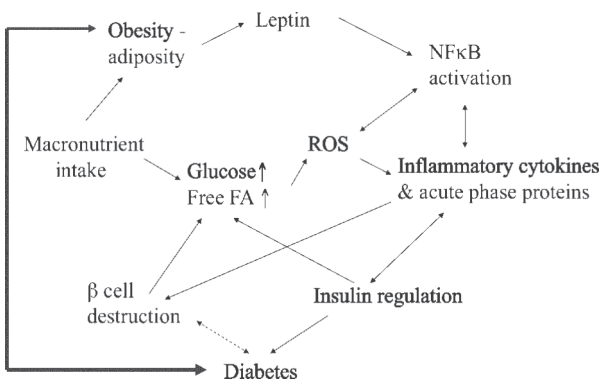

Figure 1. Proposed relations among obesity, oxidative stress, inflammation and insulin resistance.
Modified from: *TRENDS in Immunology*. 2004(Jan);25(1):4-7.

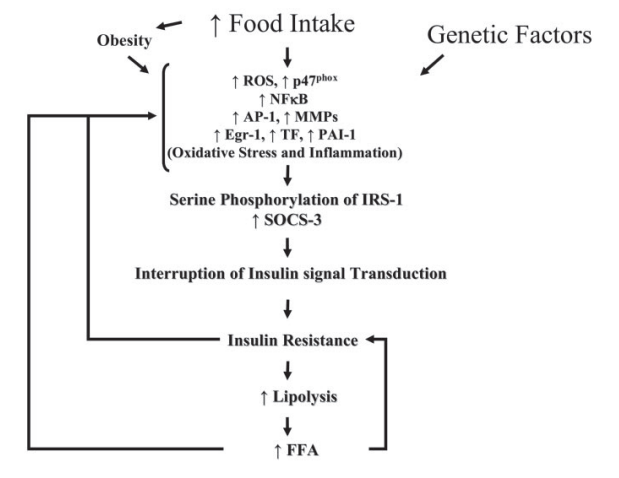

Figure 2. Pathogenesis of metabolic syndrome: inflammation hypothesis.
Circulation. 2005(Mar.22);1,452.

Relevance

As previously noted, Dandona et al. (2004) introduced the concept of obesity, ROS, inflammation and insulin resistance. Since then, interest in this interrelationship has branched out and now encompasses numerous aspects of metabolic focus. The clinical symptoms commonly associated with the complex of obesity, inflammation, oxidative stress and metabolic disease have been termed metabolic syndrome. Obesity, insulin resistance, hypertension, hyperglycemia and high serum cholesterol constitute the cluster of symptoms identifying metabolic syndrome and have been identified as high-risk factors for diabetes and cardiovascular disease in humans.

The relevance of metabolic syndrome, as defined in human medicine, is yet undetermined in our veterinary patients. Similar clinical manifestations, singularly or in combination, including obesity, abnormal circulating lipid profiles, insulin resistance, chronic inflammation, DM and other inflammatory conditions in cats and dogs,[16,17] lend support to metabolic syndromes in companion pets, particularly the overweight to obese population. Furthermore, dogs and cats have often been used as a model for human metabolic syndrome lending to obvious similarities in the pathology of and mechanisms of action associated with metabolic syndrome.[18]

A classic example, cats most often suffer from DM, which resembles type II DM in humans. Obesity and associated oxidative stress can promote insulin resistance, which are characteristically part of metabolic syndrome in humans. Can we therefore state that the obese cat with DM has metabolic syndrome? Obesity, diabetes and other oxidative stress related disease states (i.e., cancer, arthritis and asthma) are conditions that can significantly compromise pets' quality of life and shorten their life span. Whether clinical symptoms associated with conditions driven by the complex interrelationships among a pro-oxidant state, obesity, inflammation and metabolic disease fit under the umbrella term metabolic syndrome for our feline and canine patients is not the point. What is relevant is that based on human-focused research, evidence is continually emerging in the veterinary arena that supports the pointed management of obesity in companion animals to mitigate oxidative stress and collateral metabolic and inflammatory conditions.

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