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Obesity and Osteoarthritis: Causes and Management

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Abstract

Overweight and oversupplementation should be prevented in young dogs because of the deleterious effects on joint development and the potential to influence the set point for energy expenditure and calcium metabolism later in life. Overweight in adult dogs should be prevented, especially in dogs at risk of joint pathology as a result of the negative influence of leptin derived from adipose tissue on cartilage matrix and pain sensation. A weight-reduction program is the most important aspect of achieving long-lasting improvement in locomotion in dogs that are lame as a result of osteoarthritis (OA).

Glossary of Abbreviations
AGEs: Advanced Glycation End Products
GAGs: Glycosaminoglycans
IL-1: Interleukin-1
MER: Maintenance Energery Requirement
MMPs: Matrix Metalloproteinases
NOS: Nitric Oxide Synthase
OA: Osteoarthritis
OCD: Osteochondritis Dissecans
PG E2: Prostaglandin E2
TENS: Transcutaneous Electrical Nerve Stimulation
TIMPs: Tissue Inhibitors of Matrix Metalloproteinases
TNF-α: Tumor Necrosis Factor-α

Introduction

Nutrition plays an important role in OA in dogs, both as a causative factor and as a powerful therapeutic modality. Owners tend to overfeed their pets, and dietary deficiency is rarely seen in companion animal practice. When it occurs, it is mainly due to the feeding of unbalanced homemade diets.[1] In contrast, overfeeding of balanced foods[2] or oversupplementation with minerals[3-5] is seen more often. Excessive calcium intake (either with or without other constituents) is associated with disturbances in endochondral ossification and in bone remodeling in large-breed dogs.[4-6]

Disturbances of endochondral ossification can lead to osteochondritis dissecans (OCD), fragmented coronoid process and retained cartilage cones in growth plates with short radius or radius curvus syndrome, elbow incongruity and ununited anconeal process in some cases, as revealed from well-controlled studies[2,4,6-8] and a survey of clinical cases.[9] The occurrence of these potential causes of OA in young dogs of certain breeds stresses the importance of quantitative and qualitative food control.

Disturbance in bone remodeling can lead to spondylomyelopathy (i.e., canine wobbler syndrome)[2,6] and panosteitis (enostosis).[2,4,10] The risk of panosteitis is increased if puppies are given too much puppy milk replacer before weaning (<4 weeks of age) or food with a high-calcium content (i.e., 3.3% instead of 1.1% calcium on a dry matter basis) during the partial weaning period (i.e., 3 to 6 weeks of age), which causes the risk of panosteitis at an older age.[4,11] In addition, an excessive intake of calcium during a limited but vulnerable period in early life may lead to alterations, perhaps permanent, in the set point of calcium regulation.[12]

Differences in the growth curves of puppies may be caused by differences in birth weight and are not necessarily due to the consumption of excess calories in relation to the needs of the growing puppy (Figure 1), although

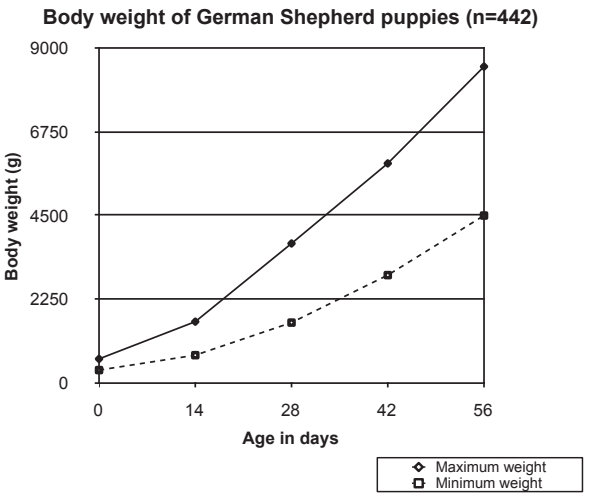

Figure 1. Growth differences in the heaviest and lightest dogs in a survey of 442 German Shepherd Dog puppies during the first two months of life raised on bitch milk and additional milk replacer for the first three weeks and more solid food thereafter.[11]

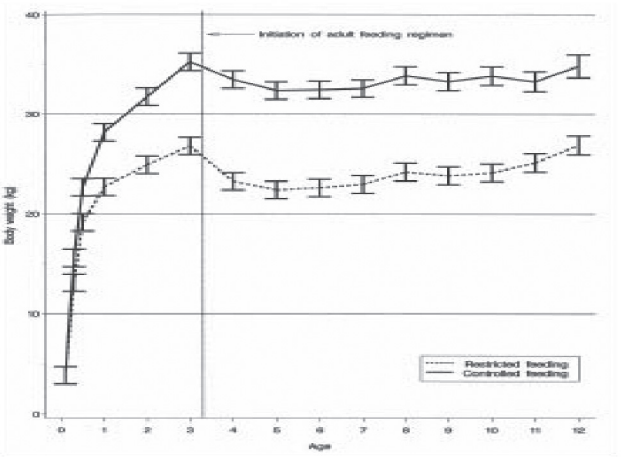

Figure 2. Differences in body weight between two groups of Labrador Retrievers (gender matched) raised on ad libitum or 75% of ad libitum calories food until 3.25 years of age and a fixed amount (62.1 Kcal/kg estimated ideal body weight) and 75% of that amount, respectively, thereafter.[13]

excess energy intake at young age obviously causes overweight at older age (Figure 2).

Obesity is a hereditary trait. The hereditary estimate for weight is approximately 0.40 to 0.70 in monozygotic twins but only 0.30 to 0.40 in dizygotic twins.[14] We demonstrated a heritability estimate for weight of 0.34 ± 0.22 (mean ± se) in a cohort of Golden Retrievers; van den Berg et al. (2010)[15] and Helmink et al (2001)[16] reported a heritability estimate for weight of 0.44 ± 0.07 in Labrador Retrievers, a breed recognized as prone to overweight.[17] The hereditary aspect also has been proposed for other breeds.[18,19]

Since obesity is a polygenetic trait, individual genes will contribute, to a lesser or greater extent, to an individual animal's response to environmental factors such as nutrition and physical activity. The identification of these genes, as investigated in our study of candidate genes in overweight Golden Retrievers,[15] may be seriously hampered by epigenetic mechanisms,[20] since gene expression *in utero* and in neonates is not related to DNA sequence alone but also to perinatal nutrition and the maternal energy and endocrine status.[21] To date, a particularly vulnerable period in puppies for influencing the set point of energy expenditure has not yet been identified in contrast to the set point for calcium metabolism in newborn puppies as described above.[4,12]

Body composition can differ per breed,[22] but in most breeds, bitches[17,18] and neutered dogs[17,23] are overrepresented in the group with obesity. In addition to genetic and epigenetic factors, metabolic imprinting (i.e., the process by which a stimulus during a critical period of development has long-term effect) plays a role. Increasing age in dogs, in contrast to cats,[24] is also correlated with increasing body weight.[17-19,25,26] The incidence of overweight can be influenced by early neutering,[17,27] orthopedic diseases (thus decreased activity), or the socioeconomic circumstances of the owner.[27,28]

Unique longitudinal studies have been performed by Dr. Kealy and Dr. Lawler at the Purina Research Institute.[13,29,30,31] In these studies, Labradors were housed with a littermate of the same gender and were allowed to feed *ad libitum* (group A, n=24) or were given a diet consisting of 75% of the calories of group A (group B, n=24). These two groups with similar genetic background (all Labradors, originating from seven different litters) and housed in the same wards and fed on the same food (although in another quantity) were compared from 8 weeks to 12 years of age. Radiological studies revealed that orthopedic diseases occurred more often and in more severe form in the overweight group A than in group B at the age of 5 years, whereas the occurrence of orthopedic diseases associated with age-related joint degeneration was more similar in the two groups of dogs at the end on the study period.

Overweight and OA

Articular cartilage is made up of a limited number of chondrocytes (<5%), extracellular matrix (20 to 30%, mainly proteoglycans and collagens [1:10 on dry matter weight]), and interstitial water (60 to 80%). The chondrocytes are most active in the superficial layer, where they are responsible for the synthesis and deposition of matrix components. Proteoglycans (mainly aggrecan) consist of numerous repeating units of glycosaminoglycans (GAGs) linked to a core protein. GAGs are negatively charged, so they attract water and cations, creating an osmotic pressure gradient that can cause cartilage to swell.[32]

Collagens (mostly type II) are organized in a fibrillar network and are cross-linked to form fibrils together with other macromolecules; these fibers restrict the swelling of cartilage, which results in tensile strain within the collagen network.[32] The fibers are anchored in the calcified cartilage at the cartilage-subchondral bone interface and run in arcades, i.e., perpendicular to the superficial zone, whereas their course is parallel to the articular surface. Damage to collagen arcades is more critical to the maintenance of cartilage integrity than a decrease in proteoglycan content because of a difference in turnover rate; for collagen, this is 120 to 350 years (!), and for proteoglycans, it is three to 1,800 days, depending on the animal's age.[33] Once damaged, collagen arcades cannot be repaired even though the synthesis of collagen by chondrocytes is increased.[33,34] The loss of collagen arcades leads to a loss of shock-absorbing capacity and

impairs the circulation of nutrients and waste products in the articular cartilage. In addition to collagen damage, cross links are no longer functional, so the cartilage has a diminished tensile strength and compressive stiffness, resulting in further loss of mechanical strength.

Although OA is a multifactorial disorder, involving genetic, environmental, metabolic and biomechanical factors, the final outcome is characterized by rupture of the collagen network, depletion of proteoglycans, clustering of chondrocytes around the lesion, and increased metabolic activity, with increased collagen and proteoglycan synthesis. Collagen is degraded by biomechanical factors and matrix metalloproteinases (MMPs), proteolytic enzymes involved in the breakdown of extracellular matrix of cartilage in normal physiological and pathological processes, accompanied by a decreased synthesis of tissue inhibitors of MMP (i.e., TIMPs).

Many of these proteinases are released under the influence of cytokines, mainly interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α). In addition, IL-1 can trigger the formation of prostaglandin E2 (PG E2). PG E2 generated in the synovial membrane induces pain, causes vasodilatation and increased vascular permeability (with more watery synovial fluid as a result), and induces proteoglycan depletion in the matrix and subchondral bone resorption. The latter can be followed by reactive bone formation, causing subchondral bone sclerosis. The damage to the cartilage matrix, the release of inflammatory mediators and proteolytic enzymes, and the decreased quality of the synovial fluid all diminish the integrity of the joint, leading to a vicious circle of cartilage degeneration (Figure 3).

With increasing age, there is a steady increase in the synthesis of aggrecan keratin sulfate and a steady decrease in the synthesis of link proteins, resulting in less stable aggregates and the formation of advanced glycation end products (so-called AGEs, mainly pentosidine). These accumulate in proteins with a long half-life, including cartilage but also dura mater, skin and lens.[35] Both processes, less stable aggregates and the formation of AGEs cause the cartilage matrix to become stiff and brittle, making it susceptible to damage when it is mechanically loaded. This phenomenon leads to *primary* OA, which is solely due to physiological aging. In older dogs with increased AGE levels, cranial cruciate ligament damage results in more severe OA, with more severe collagen damage and proteoglycan release,[36] demonstrating that *secondary* OA can be more serious in old dogs than in young dogs.

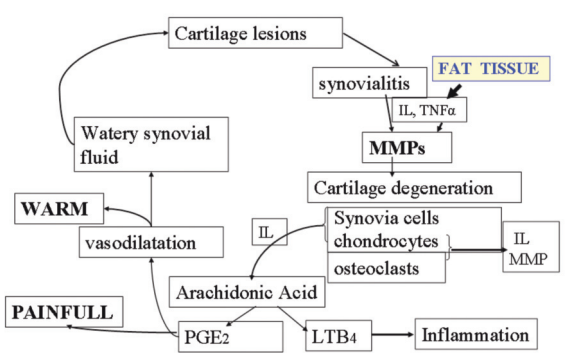

Figure 3. With primary or secondary OA as a starting point, the sequence of events depicted in this figure reveals that OA development can be blocked or slowed down by interruption of the vicious circle.

It has been suggested that overweight causes overloading of the joints, with increased joint-cartilage wear as a consequence. This is especially true in incongruent joints, where a smaller than normal joint surface bears more than the normal body weight. This supraphysiological pressure may cause extensive cartilage breakdown, with severe OA as a consequence. Joint incongruity with OA can be seen in overweight patients with hip dysplasia[13,37,38] and with cranial cruciate ligament rupture.[39,40] However, overweight was not found to be associated with OA in joints that were not incongruent because of primary disease, including shoulder OCD[41] and elbow joints[42]; however, a significant correlation between overweight and the severity of lameness due to OA could be demonstrated.[41,43]

It has recently become clear that adipose tissue is not only a storage form of excess calories but also an important source of inflammatory adipokines, including leptin, IL-1, IL-6, and TNF-α.[44] Leptin activates hypothalamic receptors, and thus regulates appetite, but also has pro-inflammatory activity. In addition, IL-1 and TNF-α are produced by activated synoviocytes, mononuclear cells and articular cartilage and can upregulate MMP gene expression. Levels of these adipokines also are elevated in joints affected by OA, and these adipokines can induce catabolic processes in chondrocytes *in vitro*, leading to cartilage matrix degradation.[45] Leptin also is produced in the joint, and leptin mRNA expression in cultures of chondrocytes derived from OA cartilage is higher in cartilage from obese men than from men of normal weight.[46] Interestingly, obese mice that are deficient in leptin do not develop signs of OA,[47] demonstrating the crucial role of leptin in the development of OA in overweight animals.

In *in vivo* studies with mice, in addition to changes due to OA, three additional effects of obesity with increased leptin levels were observed, namely, impaired musculoskeletal force, hyperalgesia and mental depression. It has,

therefore, been concluded that obesity may be a risk factor for inflammatory arthritis[45,48] and also for additional symptoms of OA. Levels of the anti-inflammatory adipokine "adiponectin," which is produced by adipocytes and by synovial fibroblasts, are reduced in adipocyte hypertrophy and adiposity, and adiponectin levels are negatively associated with OA scores in overweight mice.[45] However, chondrocytes express adiponectin receptors, and addition of adiponectin to chondrocyte cultures induces the expression of IL-6, MMP and nitric oxide synthase (NOS), all which are involved in cartilage degradation.[49] Studies have shown that mechanical loading of bovine cartilage explants inhibits cartilage matrix degradation stimulated by IL-1, which emphasizes the benefit of guided exercise and training in patients with OA.[50]

Neutralization of IL-1, and thus decrease of the upregulation of MMP gene expression or stimulation of anti-inflammatory cytokines (such as IL-4, IL-10 and IL-13), could be a novel anti-OA treatment as could growth factors that shorten the rate of collagen turnover, thereby enhancing its repair. There are high expectations of the use of stem-cell therapy to stimulate cartilage repair, but the positive effects are limited to laboratory conditions at the moment. To date, the medical treatment of OA is limited to the prevention of PGE2 production by means of either (N)SAIDs or increasing the dietary intake of long-chain omega-3 fatty acids.[51]

OA in Overweight Dogs

Several studies have shown that skeletal diseases occur more often in dogs that have consumed too many calories from puppyhood onward and that the subsequent development of OA occurs more often and is more severe in overweight dogs. The relationship between overweight and OA has been demonstrated by Kealy et al. (2000)[30] in Labradors, by Hedhammar et al. (1974)[2] in Great Danes, by Kasström (1995)[37] in German Shepherd Dogs, by Brown et al. (1996)[52] in Cocker Spaniels, and by van Hagen et al. (2005)[38] in Boxers. This also is the experience of practicing veterinarians in many dogs of other breeds and cross breeds. Overweight can be considered as the cause or the result of reduced activity, and in most cases, it can be considered as both.[55] Chronic overnutrition of pregnant mice and sheep resulted in offspring with hyperphagia, increased adiposity and reduced locomotion.[54,55]

Overfeeding rats during suckling results in obesity, leptin resistance and long-term effects on hypothalamic leptin sensitivity, possibly due to increased levels of maternal-derived leptin in the milk given to the neonate.

At a certain stage, the dog will have absorbed more energy than it requires, and the excess is stored as body fat. At the time of consultation, owners often report to their veterinarian that their overweight dog is not eating a lot, illustrating that dogs do not warrant extra energy to maintain the fat tissue. On the basis of what is known today, irrespective of the cause of overweight, we have to persuade the owner that the overweight dog should follow a weight-reduction program. The effectiveness of weight reduction has been reported in the following studies:

- Impellizer et al. (2000)[56] published a study in which nine dogs owned by clients were presented with hind leg lameness and radiographic signs of hip joint OA. These dogs were approximately 11% heavier than their ideal weight and were put on a food-reduction regimen of 60% of their maintenance energy requirement (MER). The dogs lost between 11% and 18% of their initial body weight with significant improvement in their body condition score and lameness, scored on a visual analogue scale.
- Mlacnik et al. (2006)[57] described a clinical trial involving 29 overweight or obese dogs (with body condition scores of 4/5 or 5/5, respectively) with clinical evidence of one-limb lameness and radiographic signs of OA. These dogs were put on a diet containing 60% of their daily MER, based on their ideal body weight (set at 15% less than recorded), and an owner-performed massage and exercise program. The dogs were evaluated on a force plate at set time points, and the symmetry index of peak values was determined. There was significant improvement in force plate evaluation starting 120 days after initiation of the diet and exercise program and already after 60 days with a combined weight reduction and intensive physical therapy program (with transcutaneous electrical nerve stimulation [TENS]). The weight loss was 9.3% in the weight-reduction group and 13.6% in de weight-reduction + TENS group. This difference could be explained by better owner compliance and better physical activity, because of reduced pain, in the latter group.
- In a prospective trial involving 14 obese (i.e., 20% overweight) client-owned dogs with lameness, Marshall et al. (2010)[58] demonstrated that a weight-reduction program improved locomotion (measured on a visual analogue scale) when weight loss was 6.1% or more and resulted in a better locomotion measured with force plate analysis when weight loss was 8.85% or more. This demonstrates that dogs can show improvement even before they reach their optimal body weight (Figure 4).
- Dobenecker et al. (2009)[59] reported a weight loss of 14.2% in overweight laboratory dogs administered the triglyceride protein inhibitor mitratapide without

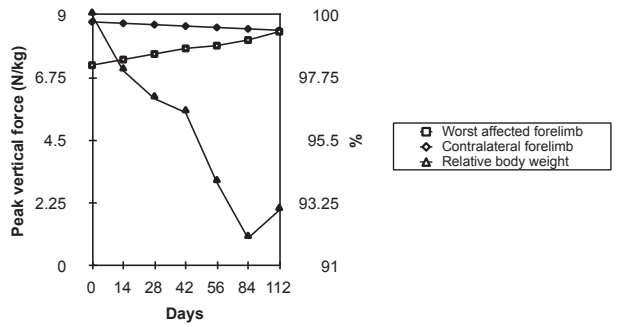

Figure 4. Weight reduction program for lame obese (i.e., 120%, of ideal weight) dogs revealed a gradual improvement of locomotion on force plate analysis of the affected leg until normal values were obtained already with a weight reduction of 6.1% (Modified from Marshall et al. 2010)[58]

food reduction and without negative side effects during the study period. We subsequently used this drug as sole therapy in overweight dogs with severe lameness and found an improvement in locomotion, objectively registered with force plate, starting at weight reduction of 7%, without side effects (Hazewinkel, unpublished results).

Total starvation has proved to be a safe and effective way of reducing the energy input, without negative side effects for a period up to four weeks in severely overweight dogs,[60] with a weight reduction in obese dogs of 20% in three weeks (n=7, client-owned dogs). Plasma albumin levels decreased, as did blood urea nitrogen, sodium and total calcium levels. Weight-reduction diets with increased protein: calorie or lysine: calorie ratio or lysine: calorie ratio enable dogs to maintain their muscle mass.[61,62]

Drugs are available to reduce fat absorption and should be taken with a normal food intake. In the future, candidate genes involved in obesity, such as MC4R in humans, should be identified in dogs and developed into pharmaceutical agents. Today, weight reduction can be accomplished with the regimens discussed at this symposium by Dr. German. Weight reduction sufficient to achieve a body condition score[63] of 5/9 or even lower accompanied by increased activity is most effective but may not be desirable if the dog has OA with marked joint pain.[64]

Although owners often find it difficult to decrease the amount of food given per meal or the number of treats given between meals,[28] they should be advised to reduce the energy intake of their dog, preferably combined with taking their dog swimming or for walks on the leash, as a way to increase energy expenditure without overloading affected joint(s). The duration of exercise should be adjusted to the effect, i.e., the dog should not become lamer after a period of rest following the leash walk.

NSAIDS, used to counteract the influence of pro-inflammatory mediators, act not only as analgesics but also prevent or slow down further joint breakdown. Neutraceuticals, physiotechniques, intra-articular injections of anti-inflammatory drugs, periarticular gold deposits or drugs meant to facilitate restoration of damaged cartilage might have a place in some cases. In cases of severe OA, when weight reduction, daily dosage of NSAIDs and lifestyle adaptations do not lead to sufficient improvement, invasive surgery might be an option.

It can be concluded that overweight of young dogs and oversupplementation of a balanced diet for young dogs should be prevented because of the deleterious effects this can have on joint development and on generalized long-lasting effects. The latter include the potential to influence the set point for energy expenditure and for calcium metabolism. Overweight in adult dogs should be prevented, especially in dogs at risk of joint pathology as a result of the negative influence of leptin derived from adipose tissue on joint cartilage matrix and on pain sensation. A weight-reduction program is the most important aspect of achieving long-lasting improvement in locomotion of dogs that are lame as a result of OA, in addition to correcting the cause of OA and anti-inflammatoiry drugs. The latter not only decreases the influence of inflammatory mediators on cartilage, subchondral bone and membrane synovialis but also increases synovial quality and decreases joint pain. The dose of anti-inflammatory drugs can be decreased when the body weight is normalized.

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