What regular column dedicated to the discussion of veterinary orthopedics would be complete without a discussion of the drugs or supplements that have been variously called chondroprotectives and nutraceuticals?

And what could be easier than to review some of the literature and provide a summary?

Plenty, for there doesn’t even appear to be a consensus on what these compounds should be called, hence the title of this article!

The most common term is “chondroprotectants,” though some argue that the term is inadequate. Many such compounds not only protect the cartilage but play a role in its repair. A “nutraceutical” has been defined by the North American Veterinary Nutraceutical Council as a nondrug substance that is produced in a purified or extracted form and administered orally to provide compounds required for normal body structure and function, with the intent of improving health and well-being (1–3, Runyon CL personal communication 2002). While some chondroprotectants could be considered nutraceuticals, others wouldn’t fit by virtue of not being in a purified form. And what of those substances that claim a disease-modifying action in the joint? Their description lies outside the definition of a nutraceutical and beyond the scope of a mere chondroprotectant. Based on the premise that there is no confusion that can’t be intensified by a good acronym, several acronyms have been coined to encompass the commonly used compounds. These include slow-acting disease-modifying osteoarthritis agents (SADMOA), structure/disease modifying antioстеoarthritis drug (S/DMOAD), and symptomatic slow-acting drugs for osteoarthritis (SYSADOA) (1).

While acknowledging the limitations of the former terminology, I will refer to chondroprotectants as that wide range of substances that affect the health of the joint positively in one or more of the following ways:

1. By stimulating and enhancing the metabolism of chondrocytes and synoviocytes, including the provision of substrate for the production of cartilage matrix and synovial fluid.
2. By inhibiting degradative enzymes and other entities, including proteases, prostaglandins, complement, and free radicals that play a role in the osteoarthritic destruction of the joint.
3. By inhibiting the production of thrombi in the microvasculature of the synovium and subchondral bone, which have been shown to play a role in osteoarthritis.

Some of these substances are oral preparations and others are injected by various routes. Some have been studied extensively in recent years, while for others, there is little information to back their claims. Although much has been learned, even more remains to be investigated. No more pressing question remains than whether the documented positive effects of certain “brand name” chondroprotectants can be extrapolated to the myriad of other products on the market that contain chondroprotectants in different forms, in different combinations, from different sources, and in different amounts. It is clear that purity, label claims, and efficacy of some products remain an issue (1,4, Runyon CL personal communication 2002).

Perhaps the most well-known and commonly-used chondroprotectants are glucosamine and chondroitin sulfate. Glucosamine is an amino sugar that is a metabolic precursor to the glycosaminoglycan, which is found in the extracellular matrix of hyaline cartilage. It has been shown to stimulate the production of collagen and proteoglycans from chondrocytes and of hyaluronic acid from synoviocytes. This leads to the repair and production of healthy cartilage and joint fluid (1,2, Runyon CL personal communication 2002). Glucosamine has also demonstrated an ability to inhibit the damaging effects of metalloproteases and collagenases from chondrocytes and of hyaluronic acid from synoviocytes. It has been credited with stimulating glycosaminoglycan and collagen production (1).

While there is agreement that glucosamine is well absorbed after oral administration, there is no agreement over whether the hydrochloride and sulfate salts of glucosamine are equivalent in this regard. One source claims equal absorption of both salts (Runyon CL personal communication 2002), another argues that the hydrochloride salt is more readily absorbed (3), while a third explains that both are absorbed but that the hydrochloride salt provides more glucosamine per unit of weight than does the sulfate form (1).

Chondroitin sulfate, the primary glycosaminoglycan in cartilage, is frequently combined with glucosamine in commercial preparations. Chondroitin sulfate reduces the osteoarthritic breakdown of cartilage by competitively inhibiting metalloproteases and by decreasing complement activation and histamine-related inflammation (2, Runyon CL personal communication 2002). It has been credited with stimulating glycosaminoglycan and collagen production (1).

Animal Clinic of Regina, 1800 Garnet Street, Regina, Saskatchewan S4T 2Z2.

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Chondroitin sulfate supplementation is also thought to prevent microthrombi formation in joint microvasculature by offsetting decreases in chondroitin sulfate that are associated with aging and are linked to microthrombi formation in the synovium and subchondral bone (2, Runyon CL personal communication 2002). The mechanisms of action of glucosamine and chondroitin sulfate are sufficiently different, such that, together, they meet all of the aforementioned requirements of a chondroprotectant. Further, there is evidence to suggest that the combination of the 2 acts synergistically (1,2). The most commonly used small animal nutraceutical (Cosequin; Nutramax Laboratories, Edgewood, Maryland, USA) (1) is the subject of the majority of published companion animal data on oral nutraceuticals (1,2,6–8, Runyon CL personal communication 2002). Laboratory and clinical trials with this product have demonstrated increased serum levels of glycosaminoglycan, increased biosynthetic activity of chondrocytes, decreased degradation of cartilage by proteolytic enzymes (6, Runyon CL personal communication 2002), statistically significant decreases in osteoarthritis scores compared with controls (7), and improvement in subjective markers of osteoarthritis, such as pain and mobility (5). It also contains manganese ascorbate, which is a cofactor in glycosaminoglycan synthesis, facilitates production of synovial fluid, and may act as an antioxidant (1,2).

Injectable chondroprotectants include a semisynthetic glycosaminoglycan derived from bovine tracheal cartilage (Adequan; Luitpold Pharmaceuticals, Shirley, New York, USA) and a semisynthetic polysulfated polysaccharide produced from beech hemicellulose (Cartrophen-Vet; Biopharm Australia, Sydney, Australia). Both have been shown to suppress the action of catabolic enzymes, stimulate the synthesis of proteoglycans and hyaluronic acid, and improve circulation to synovial membranes and subchondral bone by fibrinolytic activity on microthrombi. Indeed, while the latter effect in both products has been shown to prolong clotting times, this has not proven to be clinically significant (1,8–11, Runyon CL personal communication 2002).

Antioxidants or free radical scavengers have been touted as potential chondroprotectants due to their ability to interfere with oxidative cell damage. These substances include vitamins C and E, selenium, superoxide dismutase, and dimethyl sulfoxide. To date, information establishing safety and efficacy of some of these products in animals is scarce. In addition, many questions have been raised concerning bioavailability and quality control of commercially available products (1,4).

Hyaluronic acid is one of the glycosaminoglycan components of hyaline cartilage and is a main ingredient in synovial fluid. It has been used extensively in humans and horses, most often via the intra-articular route, although an IV form is also available. It acts by increasing the quality and quantity of synovial fluid, decreasing inflammation, and as a free radical scavenger. Use of this compound in small animals has been largely experimental to date (1, Runyon CL personal communication 2002).

Perhaps the newest use of chondroprotectants has been their inclusion in pet foods. Most often this has involved the inclusion of glucosamine and chondroitin sulfate. Controlled studies indicating the benefits of chondroprotectants in pet foods have been few and the questions remaining are many. Specifically, are chondroprotectant levels in pet food sufficient to provide therapeutic levels to most animals? What is the effect of pet food processing on the bioavailability of chondroprotectants? Does pet food processing mean that chondroprotectants are absorbed intact or as subunits, and does it matter (1,3)?

Most recently, a therapeutic joint management diet (Prescription Diet j/d; Hill’s Pet Nutrition, Topeka, Kansas, USA) has been released that claims to modify the osteoarthritic degradation of canine joints. It contains glucosamine and chondroitin sulfate, but its therapeutic effects are attributed primarily to the fact that it is high in omega-3 fatty acids, specifically eicosapentaenoic acid. The n-6 polyunsaturated fatty acid arachidonic acid is a major component of cell membranes. Under conditions of cell injury and death, arachidonic acid is liberated and is converted to inflammatory mediators via the cyclooxygenase pathway. Eicosapentaenoic acid will competitively inhibit the metabolism of arachidonic acid, producing many fewer inflammatory byproducts. Animals supplemented with or fed diets high in omega-3 fatty acids show significant decreases in joint inflammation and degenerative joint disease (1,12).

References