Meta Analysis: Glucosamine and Chondroitin, 1956-2006 Comprehensive Overview of Existing Data.

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All of the efficacious products available on the market today contain glucosamine and chondroitin as their primary active ingredients in one form or another. However after a close analysis of the existing data I am sure you will find the GLC formula to be the most complete, comprehensive and logical choice for your clients in need of oral chondroprotective care. To date there are over 200 clinical trials and published works in cross species applications validating the effective use of glucosamine and chondroitin as a disease modifying agents. Some of the most recognized human studies are as follows; the American Medical Association Quarterly, published the findings of a comprehensive meta analysis "..research demonstrated a highly significant efficacy of glucosamine on all outcomes, including joint space narrowing and WOMAC. A-4 chondroitin sulfate was found to be effective on Lequesne Index, visual analog scale pain, mobility and responding status." (1) More recently the National Institute of Health conducted a 6-month GAIT study in which glucosamine and chondroitin out performed the anti-inflammatory drug Celecoxib 79% to 69% for moderate to severe knee arthritis:WOMAC 300-400. (it should be noted: this same study did not show a statistical improvement for those with mild symptoms WOMAC 125-300) (2) Secondarily, the UB Barcelona published the Effects of Glucosamine Sulfate on 6-Month Control of Knee Osteoarthritis Symptoms vs Placebo and Acetaminophen: Results from the Glucosamine Unum in Die Efficacy (GUIDE) Trial, demonstrating glucosamine sulfate superior to NSAID's as measured in Lesequin and WOMAC peramiters. This study also helped establish a benchmark for single dose applications of glucosamine at 1500mg rather than the 500mg 3X found in previous works. Furthermore, Dr. Martha Rodgers VMD of Lexington Kentucky published an 8 year clinical trial evaluating the use of Glucosamine and Chondroitin (G/C) for equine osteoarthritis. (It should be noted that in this, the longest running evaluation on the use of G/C to date; Dr. Rodgers utilized the GLC formula for the duration of the study).This independent evaluation of G/C helped to bring clarity to the practitioner in validating both formulary and the necessary milligram levels that elicit the desired response in the equine model. (1 gram per 100 pounds of bodyweight) This is also the only trial to date that demonstrated long term clinical changes in the progression of osteoarthritis in the animal model, solidifing G/C as disease modifying agents. (4) Over the last 40 years we have been provided with a wealth of data, reinforcing the sound pharmacological principals of G/C and their application in combined human and veterinary medecine. This body of work has been the inspiration in the development of the patented GLC formula. After close review I am sure you will find GLC to be superior in composition and scientific rational as compared to other products. In addition, GLC products insure the best value for your clients and your practice.

History

In recent years a great deal of attention has been given to the use of oral chondroprotective agents and their ability to benefit cartilage and synovial tissues. The primary compositions available consist of two key ingredients: glycoproteins in the form of exogenous glucosamine (HCl, NaCL, KCl,and N-acetyl) and polysulfated glycosaminoglycans in the form of chondroitin sulfate C-6 and A-4. Each of these compounds has been researched both individually and in combination in multiple species trials as a treatment for osteoarthritic conditions, and have proven the efficacy of these orally administered agents in beneficially modifying articular cartilage and reducing degenerative enzyme secretion within the synovium. Glucosamine and chondroitin studies have been favorably conducted on a variety of species including Human, Canine, Equine, Rabbit and Rodent models; and demonstrate a similar metabolism and pharmacology between species. The disease modifying capability of these glycoproteins

and glycosaminoglycans have made them a popular therapy for the treatment of osteoarthritic conditions. A brief overview of these agents and the tissues involved will help to familiarize you with the history, use and application.

Glucosamine

Glucosamine esters were first identified as an important tissue modifier within the body in the late fifties.(Roden 1956) This naturally occurring glycoprotein was found to be present in body tissues, with the highest concentrations present in the synovial and cartilage matrices. Trace levels are extracted from food sources and converted via digestive protein synthesis and the hexosamine glucose pathway into the active ester form glucosamine 6 phosphate.(1, 2) Research demonstrates the presence of glucosamine esters to have a direct and beneficial effect on articular cartilage regeneration, by stimulating the two groups of cells responsible for cartilage and hyaluronan maintenance and production; chondrocytes and synovicytes (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14) When exposed to elevated serum glucosamine, the synovium is benefited through two methods of action. Chondrocyte cells within articular cartilage, react in an anabolic fashion by producing more collagen, proteoglycans (the key structural matrices of fibril, hyaline and articular cartilage) and hyaluronan (the viscous lubricant which bathes and nourishes the synovium) Synovicytes and synovial cells are responsible for nutrient passage and primary regulation of hyaluronic acid within the synovium. Scientists also discovered that the amount of glucosamine present have a direct effect on the ability of the chondrocytes and synovicytes to accelerate the production of these key components. Under normal conditions the cells maintain equilibrium to regulate proper cell function. Chondrocytes monitor the condition of the cartilage through cilium “probes” extending into the matrix. Changes in the condition and integrity of cartilage tissues, signal the response to regulate net growth, remodel or maintain equilibrium. Synovial cells respond directly to serum protein concentrations and allow passage of nutrients through the synovial membrane via free diffusion. When a greater than normal glucosamine phosphate presence is detected, these cells respond in an anabolic fashion, through increased production of proteoglycans, collagen and hyaluronan. (3, 4, 6, 10, 13, 14). These findings led to the development of stabilized exogenous forms in 1972 by the Italian researcher, Rovati. His patented sulfated forms of glucosamine were the first to make oral supplementation possible.

Currently bioavailable oral glucosamine has been isolated and stabilized in three anion forms, glucosamine sulfate sodium (+NaCl), glucosamine hydrochloride (+HCl), glucosamine hydroiodide, one cation form, glucosamine sulfate potassium (-KCl) and one neutral acetyl form N-acetyl D-glucosamine (GLNAdl). While all are viable; only the hydroiodide form is not well tolerated orally. The pharmacology of glucosamine in these exogenous forms is fairly well understood and absorption rates documented at 86% and 98% for glucosamine sulfates, using radio isotope markers 14C and standard urine and fecal sampling. (15, 16, 17) Absorption and utilization are achieved following two specific paths of active and passive diffusion via digestion. Through active diffusion highly soluble chloride and acetyl are utilized entirely through enzymatic conversion and mucosa passage (18, 19, 20, 21, 22) Sulfates undergo similar enzymatic conversion, yet they maintain some ion and sulfate retention. At primary conversion, the available exogenous glucosamine is cleaved from its anion host by hydrochloric acid and digestive juices in the first pass through the stomach. From there enzymes in the small intestine convert the glucosamine to its usable ester which passes to the bloodstream in its most anabolic form glucosamine 6 phosphate and glutamine isolates (1, 15, 23) Through secondary and passive diffusion the remaining sulfate anion and cation glucosamines, are carried via portal transfer to the liver. In this stage secondary enzymatic conversion takes place releasing the usable sulfur and phosphate esters systemically.(30) Trace elements of remaining exogenous sulfate glucosamine permeates digestive membranes and passes through the body retaining its original ion charge sodium (+NaCl) potassium (-KCl). It is hypothesized that the relationship between these particle charges; specifically

glucosamine bound to sulfate sodium and sulfate potassium may facilitate nutrient ionic transfer between target cellular membranes and allows a greater cellular uptake of the available glucosamine esters. GLC is the only glucosamine combination which addresses this mechanism to increase membrane permeability and secondary utilization. The assimilation of glucosamine in the sulfate form through both active and passive diffusion is detectable via radio marker and UA; these diagnostic measures show a peak serum level within 2-4 hours and a rapid decline after 8-10 hours from first ingestion. Trace amounts may be present for as long as 36 to 48 hours in route to articular cartilage tissues (15,16,17,18,19) The desired anabolic response by both chondrocytes and synovicytes is in direct relation to the available serum and tissue glucosamine; only by providing a sufficient quantity of bioavailable glucosamine in a timely regimen can we take full advantage of the opportunity for accelerated reparation and reaching the rate-limiting threshold. The necessary quantity for chondroprotection may very between species due to minor variances in enzymatic systems and the species ability to identify and utilize glycoproteins and glycosaminoglycans. Existing clinical data for multiple species trials fall within parameters ranging from 50/800mg per KG for glucosamine supplementation (GS 24,25,26,27,28,29,31,32, GL&CS 33,34,35,36,37,38,39). These quantities have established the minimum effective standard baseline for use in the multiple species models. Extrapolation of this data indicates similar effective dosing levels as those advocated with GLC products in a 3-to-1ratio of glucosamine and chondroitin (1-gram per 100 pounds for equine, 1-gram per 75 pounds for human and 1-gram per 50 pounds for canine) Many products today advocate use of these proven levels for a short period of time, calling the proper levels a “Loading Dose” These same products will then advocate a reduced level be used after symptoms lessen, usually after 3-4 weeks. Unfortunately there is NO scientific data showing these trace quantities to be effective. To the contrary, two studies have shown these “maintenance levels to be no more effective than placebo in equine trials. Another misnomer, which must be dispelled, is the gratuitous claim that glucosamine hydrochloride is the most bioavailable and most studied glucosamine form, this is easily disproved by the existing clinical data. While rapidly assimilated in the small intestine; this form is rapidly metabolized and removed from available serum levels indicating a necessity for more frequent application. All independent research from Rovati in 1972 to the recent British Lancet have proven glucosamine sulfates to be the most efficacious forms available to the body, and the only forms demonstrating proven assimilation via radio labeled 14C markers.

Chondroitin Sulfate

When articular cartilage becomes compromised; the chondrocytes excrete degenerative enzymes in order to remove the affected tissue so it may be replaced by healthy new cartilage. Under normal conditions this process maintains equilibrium; however through compressive failure, trauma or aging; an imbalance occurs and the degenerative process accelerates the onset of osteoarthritis. Chondroitin sulfate; specifically chondroitin 4-sulfate type A, has the potential to reduce the excretion of metalloproteinase; the primary degenerative enzyme inside the synovium.(40,41,42,43,44) Chondroitin sulfates belong to the family of mucopolysaccharides; more specifically glycosaminoglycans and proteoglycans, and fall into two separate categories; Chondroitin Sulfate C-6 and Chondroitin Sulfate A-4. Chondroitin sulfates are one of the major components of the proteoglycan network which provide the compressive resilience of articular cartilage The close netting of negatively charged proteoglycans give articular cartilage the ability to bind and release positively charged water molecules keeping the matrices properly hydrated. Chondroitin sulfate, along with keratin sulfate and hyaluronan bind to collagen to form articular cartilage. In their purified exogenous form, chondroitin sulfate A-4 is comprised of two compounds galactosamine and glucuronic acid. The primary role of chondroitin sulfate A-4 in promoting joint health lies in the ability to reduce the degenerative enzymes metalloproteinase, bind water into the cartilage matrix and provide the basic raw material, which comprises articular cartilage. It is theorized that by

increasing the available pool of glycosaminoglycans via oral ingestion of chondroitin sulfate, the chondrocytes will be facilitated in their synthesis of proteoglycans thus aiding in the reparation process. This theory has proven accurate in modifying tissues and reducing clinical symptoms in both human and animal models (CS 45,46,47,48,49,50,51,52). It should also be noted that injectable polysulfated glycosaminoglycans such as Adequan have proven efficacious in numerous studies.
The main controversy surrounding the use of chondroitin sulfates revolve around the molecular structure and bioavailibility of the two materials, CS C-6 and CS A-4. Chondroitin Sulfate C-6 is a broad category primarily consisting of crude muchopollysaccharides such as shark cartilage, porcine, chicken cartilage, perna canaliculus, and skin tissues, keritin and dermatin sulfates. Poor absorption rates of CS C-6 are due to the large complex structure of the molecule and the existing cohesive bonds of the collagenous material binding the galactosamine and glucuronic acid thus preventing efficient digestive cleaving. To date chondroitin sulfate C-6 has not been proven to demonstrate bioavailability through digestive pathways; or metabloisim through serum testing. Chondroitin sulfate A-4 is refined using collagenase; eliminating the cohesive bonds and allowing a specific constitution of galactosamine and glucuronic acid to be produced, providing a small enough molecule for intestinal passage of both the intact CS A-4 and substrates. The pharmacology of chondroitin sulfate A-4 provides active enzymatic first pass diffusion through intestinal membranes detectable by both serum evaluation and disaccharide content.(52,53,54,55,56,57). Radio labeled chondroitin sulfate A-4 demonstrates favorable systemic absorption present in the liver, kidney, synovial fluid and cartilage tissues via digestive pathways.(58) This cross species test using radio markers as the primary diagnostic tool indicated a greater metabolic availability for carnivore, omnivore and herbivores in descending order.
The latest twist to the chondroitin controversy revolves around molecular weight. The process for extracting and isolating chondroitin sulfates has improved and so has the quality of the material. Current molecular weights vary from 5kDa to 20kDa. and are dependant upon the quality of raw material and manufacturing process. A recent study funded by Nutramax suggests that the lower the molecular weight of the material, the greater the permeability.(CS 17) The study used serum plasma disaccharide counts as the marker to suggest absorption of two A-4 materials provided by the Bioiberica company. According to the analysis, absorption rates of experimental 8kDa material were 32% and the Cosequin16.5kDa material at 22% for equine administration. Using this same model as the basis for comparison, you will be happy to know, all GLC products contain the patent pending Opta-flex solvent free chondroitin sulfate A-4 produced by the Cargill company. This unique process for manufacturing chondroitin sulfate has proven to provide the purest and most bioactive form currently available; demonstrating molecular weights equivalent to and lower than that of the Bioberica material. The methodology and advocated administration rates of GLC products provide more active chondroitin sulfate per dose, insuring even greater absorption of the available material. All GLC chondroitin sulfate are tested and verified by both manufacturer and independent laboratory analysis using the worlds most respected testing authority, Alpha Laboratories;a division of Eurofins demanding; HPLC standards of 90% or better and USP proposed CPC titration of 95% or better. We use only U.S. origin material to insure a BSE free source.
The GLC formula delivers the only product line which addresses the synergistic relationship between chondroitin sulfate and N-acetyl D-glucosamine. This unique combination of oraly administered chondroitin sulfate and N-acetyl D-glucosamine, provides metabolic precursors necessary for HA production. Hyaluronic acid is made up of two key substrates; glucuronic acid and N-acetyl D-glucosamine (59). When broken down via active diffusion, chondroitin sulfate provides one of the key components for hyaluronan in the form of glucuronic acid (52). The addition of N-acetyl D-glucosamine present in the GLC formula, provides both hyaluronan precursors in one complete composition.

Proper Dosing

There has been a great deal on confusion as to the proper dosing for G/C in regard to species and body weight. A review of the existing data exhibiting efficacy and examining the toxicology studies provides insite. The GLC formula contains a 3 to 1 ratio of glucosamine complex to A-4 chondroitin sulfate. The following studies help us to better understand the proper use and dosing of G/C in carnavores, omnivores, and herbavores and are the scientific rational for the advocated dosing found in GLC products. It has been demonstrated that glucosamine is well absorbed and has a similar metabolic fate in multiple species (15,16,17) yet the effective mg/KG ratio varies between species; Glucosamine Studies: Equine: 16mg/KG (35, 60) Canine: 65mg/KG (61) and Human: 36mg/KG (62) GLC Advocated Levels: Equine 16mg/KG, Canine: 60mg/KG and Human: 43mg/KG

Chondroitin Sulfate A-4 has a varied rate of absorption and it's metabolic fate changes due to the enzymatic differences between species. Radio marker and disaccharide testing proves this to be true. Canine 70% (58) Human 50% (56) and Horses 22% (53) With this information in mind it is logical to draw the conclusion that carnivores will require lower milligram levels of chondroitin sulfate as compared to that of herbavores, in order to elicit similar beneficial effects in practice. This is why GLC advocates slightly lower levels of chondroitin sulfate for carnivor and omnivore applications. Chondroitin Sulfate has been studied at an effective rate that varies among species as well.

Chondroitin Studies: Equine 5mg/KG (60) Canine: 37mg/KG and Human: 14mg/KG (45) GLC Advocated Levels: Equine 5mg/KG, Canine: 21mg/KG and Human: 11mg/KG