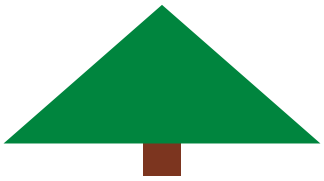
Canine Osteoarthritis: Evidence Based Proof of the Disease Modifying Properties of Calcium Xylopyranose Polysulfate

sylvet
capsules



sylvan

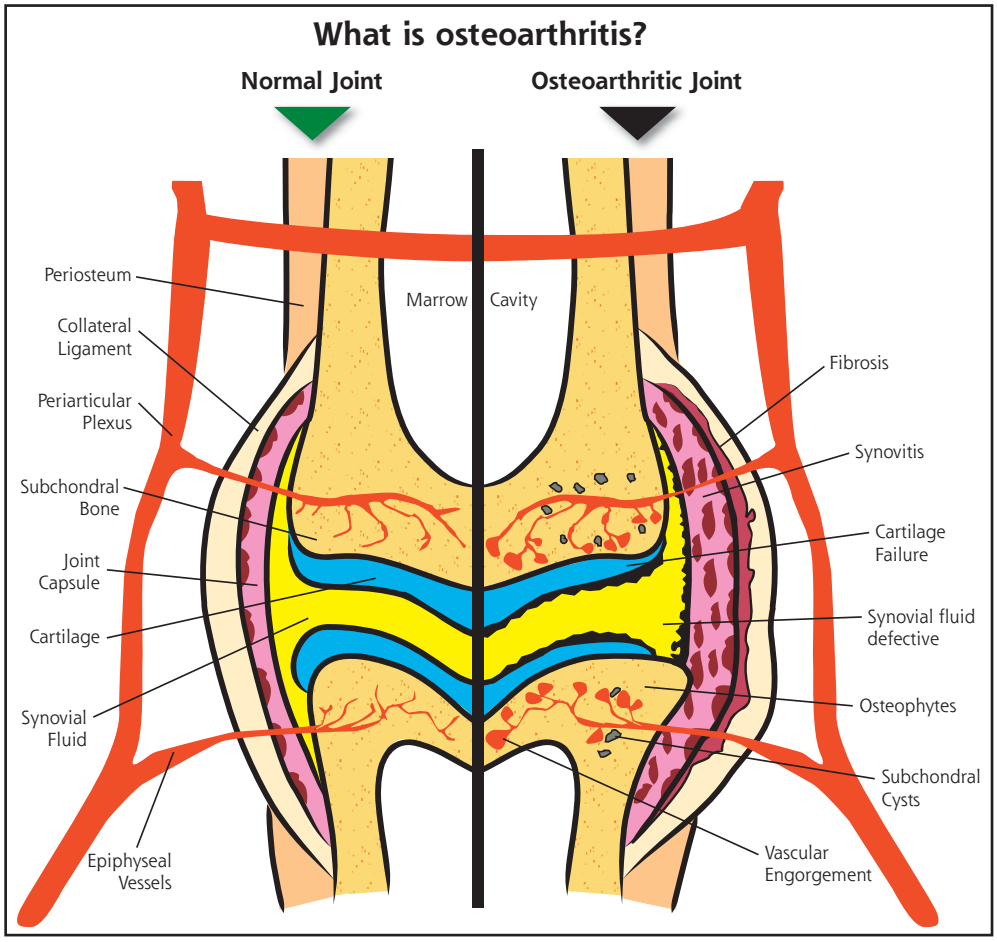
A fabled deity or spirit of the woods.
(L *sylvanus*, from *silva* forest)

CONTENTS

The degenerative effects of osteoarthritis (OA) on the joint

Articular cartilage and synovial fluid are essential components for the optimum mechanical performance of synovial joints, and the failure of these tissues in the various arthritides is contributory to the perpetuation of this group of diseases.

In normal "healthy" joints, the articular cartilage which covers the ends of the long bones, in conjunction with synovial fluid, provides an almost frictionless, wear resistant, weight-bearing surface. The articular cartilage also dissipates most of the contact stresses acting across diarthrodial joints during loading, thereby more evenly distributing the forces which are transmitted through subchondral bone. Synovial fluid is often decreased in quality (viscosity) in osteoarthritis (OA) due to defective hyaluronic acid synthesis and increased catabolism. This leads to a decrease in lubrication and stabilisation of the joint resulting in additional cartilage trauma and wear. There is hypoxia, decreased pH, and accumulation of lactate in synovial fluid of arthritic joints.



An early event in the pathogenesis of OA is softening and fibrillation of articular cartilage. This results in a decline in its functional capacity and, under normal weight-bearing conditions, abnormally high contact stresses are transmitted to focal areas of the articular cartilage and subchondral bone, exacerbating the damage to these tissues. The cartilage fragments and matrix degradation products (e.g. from proteoglycans and type II collagen) released from the damaged articular cartilage are antigenic and when they localise in the synovial membrane, they can provoke an inflammatory response (synovitis). Once the synovitis becomes established in the joint, the synovial lining cells together with leucocytes recruited from the blood, release a host of noxious substances which can perpetuate the OA processes. These include proteinases, prostaglandins, cytokines (IL-1, TNF-$\propto$) and free radicals, all of which can directly and indirectly degrade cartilage, bone and the hyaluronic acid of synovial fluid.

Cartilage derived antigens released into synovial fluid can also activate blood leucocytes to express pro-coagulant and cytokine activities. This may result in deposition of lipid and fibrin clots in synovial tissues and in the small blood vessels supplying the subchondral bone. When blood flow and nutrition to bone and synovial cells is compromised by these occlusions the result is ischaemia, cell necrosis and joint pain. Furthermore, in response to the cellular necrosis and trauma, there is remodelling and thickening of subchondral bone altering its mechanical compliance. This increases the load-bearing stresses carried by the overlying articular cartilage, thereby subjecting it to excessive mechanical stresses. These mechanical factors all contribute to cartilage failure in OA.

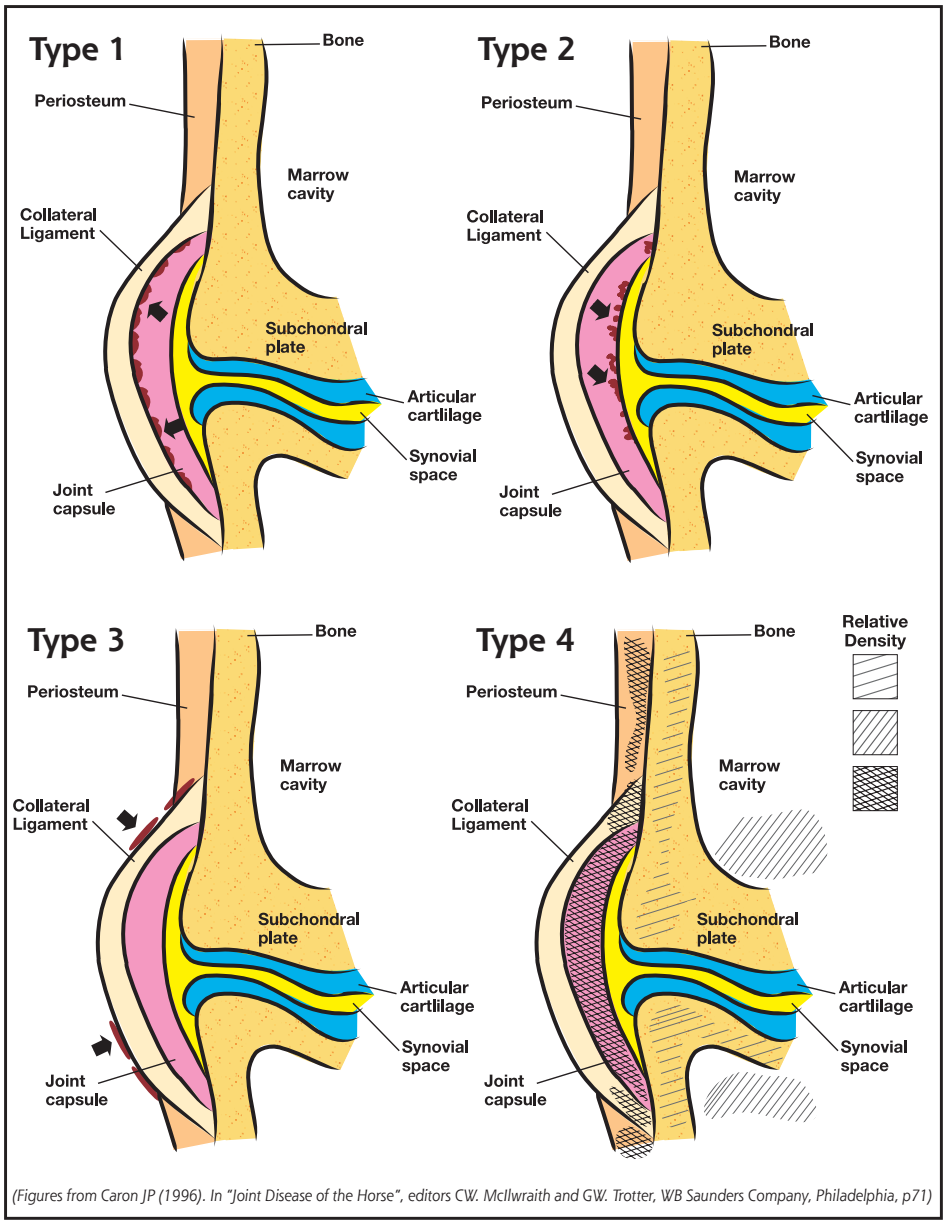
A variety of therapeutic agents are available for the treatment of OA but steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) are the most extensively used today. While the potent anti-inflammatory and analgesic activities of these agents may reduce the symptoms arising in OA joints, chronic use of some NSAIDs and corticosteroids have been reported to accelerate joint destruction largely due to the inhibition of cellular anabolic processes. The adverse effects of NSAIDs on the gastrointestinal tract, liver and kidney are well documented. COX-2 NSAIDs, thought to be safer than traditional NSAIDs, are associated with hidden pitfalls including adverse effects on the healing of bone, cartilage, eye, ligament, skin, tendon, tendon to bone and cardiovascular function.

OA and pain

Pain in domestic animals has been defined as an aversive sensory and emotional experience manifesting as an awareness by the animal of damage to or threat of damage to the integrity of its tissues. This results in a change in the animal's physiologic responses and behaviour to reduce or avoid damage, to reduce the likelihood of recurrence and to promote recovery. Anil SS, *et al.* (2002). *JAVMA*. 220: 313-319.

Pain in OA is the most important clinical sign in humans and domestic animals. Pain is the principle cause of reduced performance and its pathogenesis is usually multifactorial. Control of pain is a key objective in the management of OA, however, this must be balanced with the important role the peripheral neuroanatomy of joints and pain plays in preventing further damage. In addition, the other objectives of OA treatment must also be addressed, including (1) regain normal joint function, (2) prevent cartilage destruction, (3) prevent fibrosis to preserve joint range of motion, (4) control inflammation, (5) prevent subchondral bone changes and osteophyte formation, (6) maintain a normal biochemical environment within the joint and (7) preserve synovial fluid viscosity and chemical makeup. McLaughlin R (2000). *Vet. Clin. North Am: Sm. Anim. Pract.* 30: 933-949.

The peripheral neuroanatomy of joints is reported to be similar in many species and the popular classification of articular nerve endings in mammalian appendicular joints is four receptor types – types 1, 2, 3 and 4. Note the absence of nerve tissue in articular cartilage.



(Figures from Caron JP (1996). In "Joint Disease of the Horse", editors CW. McIlwraith and GW. Trotter, WB Saunders Company, Philadelphia, p71)

Type 1 – mechanoreceptors located in the superficial areas of the joint capsule; low-threshold and stimulated by relatively mild mechanical stimuli; remain active while a mechanical stimuli persists;

Type 2 – mechanoreceptors located more deeply in the joint capsule; low-threshold and rapidly adapting; inactive when joints are immobile and activated when joints undergo movement or experience tension;

Type 3 – mechanoreceptors are large and are restricted to intra-articular and periarticular ligaments near their insertions; high-threshold and slowly adapting; inactive in stationary joints and with active and passive movement over a limited range; activated only when joint excursions occur near physiological limits or when ligaments containing them undergo powerful traction forces; capable of nociception and modifying type 1 and 2 receptor-mediated reflexes; and

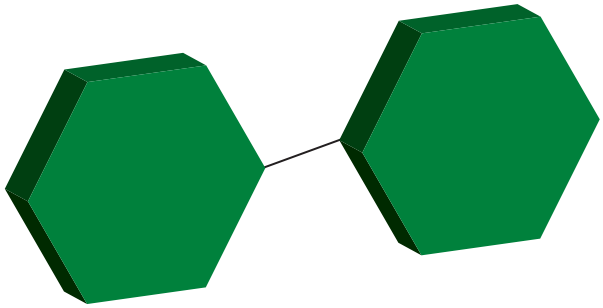
Type 4 – 'receptors' are free nerve endings rather than specific end organs like receptors 1 to 3 of which there are two types – type 4a and 4b; high threshold and slowly adapting nociceptors; activation signals impending or actual tissue damage; are polymodal and respond to mechanical, heat and chemical stimuli such as lactic acid, kinins, serotonin, histamine and prostaglandin E_2.

Pain management is important in OA treatment, however, the protective and restorative roles played by pain must be acknowledged to avoid compromising the other objectives of the treatment of OA. Therefore, treating the disease rather than the sign(s) of disease (eg. pain) minimises risk of further injury and maximises potential recovery (eg. with cruciate ligament strain/partial rupture).

The evolution of CaXPS

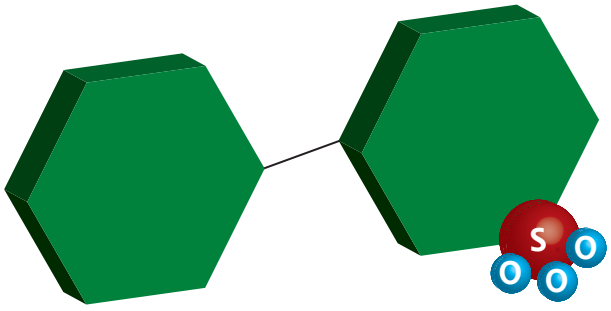
1. Unsulfated Polysaccharides

Unsulfated polysaccharides first evolved in single cells such as bacteria and fungi. There are no sulfates on these molecules. They play a protective and structural role around cells. Examples are hyaluronan which acts as an intracellular glue in mammals and bacteria and xylopyranose which form part of the structures of many grasses and woods. Hyaluronan is used as a cosmetic and for the treatment of arthritis by injection into the joint. Xylopyranose, the backbone of Calcium Xylopyranose Polysulfate (CaXPS), is the same as the dietary component in "soluble fibre" and as such is used as a food supplement.



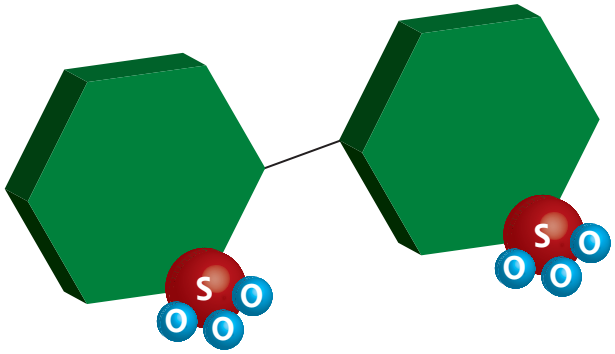
2. Sulfated Polysaccharides

Sulfated polysaccharides evolved in multicellular organisms. There are one or two sulfates every two sugars. They are wide spread in connective tissue as structural components as well as on the surface of cells where they affect and bind proteins which can then act on the cell metabolism. Examples include chondroitin sulfate which plays a role in connective tissue structure and heparan sulfate which plays a role in stabilising cell receptor complexes. Chondroitin sulfate is widely used as a nutraceutical for arthritis.



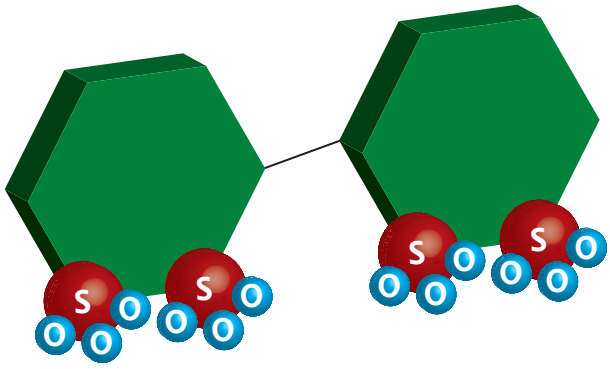
3. Highly Sulfated Polysaccharides

Highly sulfated polysaccharides evolved to control the inflammatory reaction to parasites in mammals. There are two to three sulfates every two sugars. They are restricted to cells of the inflammatory system called mast cells, basophils and eosinophils. The highly sulfated molecules are released from granules in the cell when required. Examples are heparin and chondroitin sulfate E which have anti-inflammatory and immune modulating activities. Heparin and its fractions are widely used as a pharmaceutical anticoagulant.



4. Over Sulfated Polysaccharides (synthetic)

Over sulfated polysaccharides such as CaXPS are only made by chemical synthesis and are not seen in nature. There are three to four sulfates every two sugars. The result of the higher charge on the over sulfated molecule is that it will displace a lesser sulfated molecule such as sulfated or highly sulfated polysaccharide from a receptor or binding site on a protein thus changing the protein's activity. Examples are CaXPS and sodium pentosan polysulfate (NaPPS) which are used in the treatment of various inflammatory conditions such as arthritis.



Sylvet Capsules affect the underlying metabolic abnormalities of OA

They alleviate the clinical signs of OA by acting on a number of pathways responsible for its pathogenesis.

Sylvet Capsules contain CaXPS which is also known as calcium pentosan polysulfate. CaXPS is a semisynthetic polysulfated polysaccharide that possesses disease modifying and anti-arthritic chondroprotective properties. Sylvet Capsules have been shown to exhibit the following actions:

(a) Stimulates chondrocytes to synthesize cartilage matrix;

(b) Stimulates synoviocyte biosynthesis of hyaluronic acid;

(c) Inhibits and modulates pro-inflammatory mediators, bio-active amines such as: histamine, serotonin, superoxide free radical, enzymes such as elastase, hyaluronidase, cathepsins, TNF-∝ converting enzyme (TACE) and proteins of the complement system which are implicated in the degradation of cartilage matrix components;

(d) Mobilizes thrombi and fibrin deposits in synovial tissues and subchondral blood vessels, thus increasing the perfusion of the joint, with resulting improvement in nutrition;

(e) Mobilizes lipids and cholesterol in synovial and subchondral blood vessels;

(f) Strong anti-inflammatory properties which act at the cellular and humoral level;

(g) Desensitises platelet aggregation and clotting;

(h) Increases the levels of natural inhibitors of metalloproteinases in cartilage;

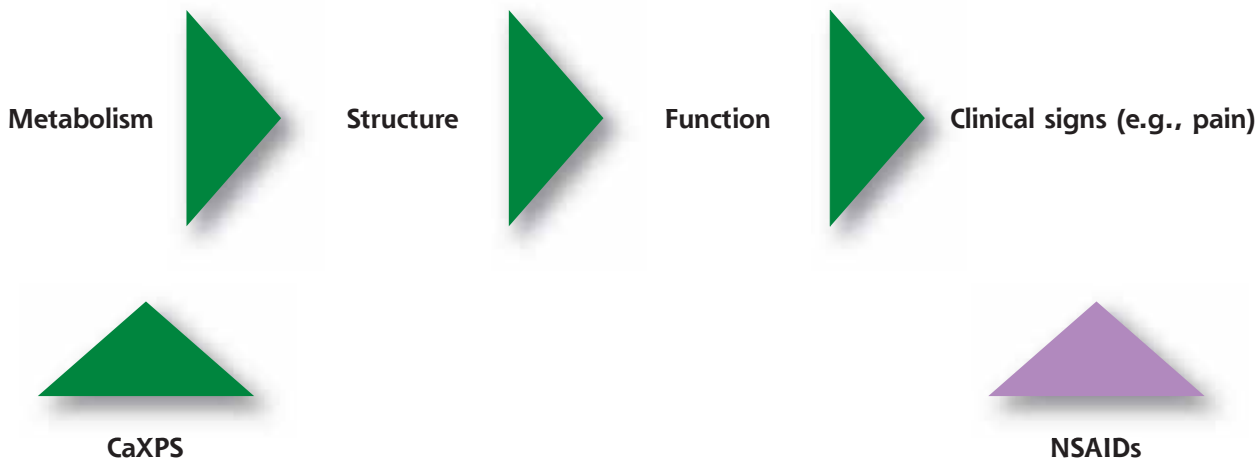
(i) Stimulates plasma levels of tissue plasminogen activator and decreases plasminogen activator inhibitor, which improves clot dissolution;

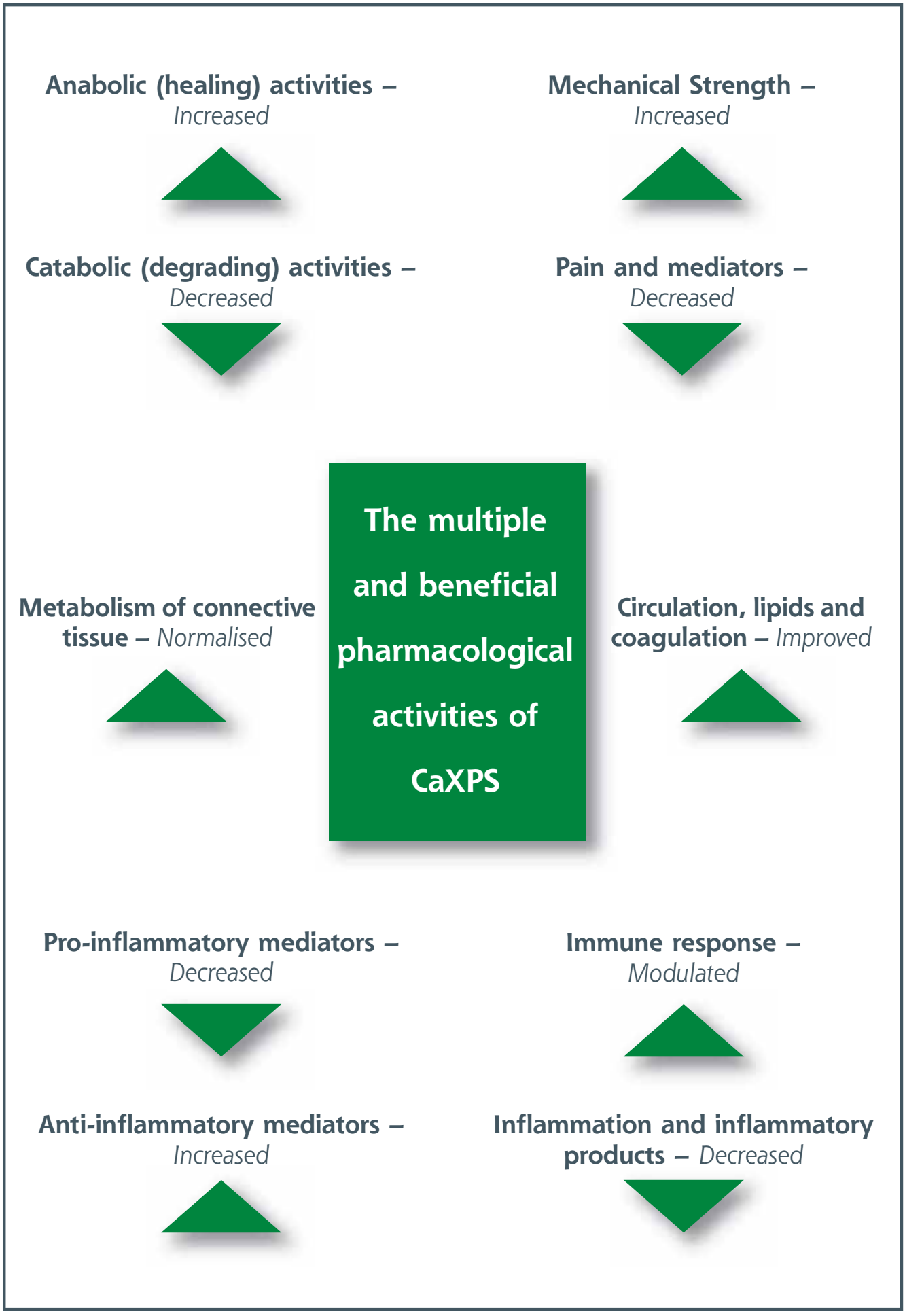
(j) Increases plasma lipase levels.

While Sylvet Capsules will benefit acute through to chronic OA, due to the progressive nature of this disease, early intervention with Sylvet Capsules in acute injuries that respond clinically as connective tissues regain normal performance is desirable.

In man, pentosan polysulfate has been shown to selectively recruit lymphocytes into the circulation and modulate the expression of mononuclear cell procoagulant activity. The ability of pentosan polysulfate to activate the immune system assists in the correction of the coagulation defects of OA and helps reduce clinical signs e.g. pain. Anderson JM *et al*. (1997) *Current Therapeutic Research.* 58(2): 93–107

Mode of action

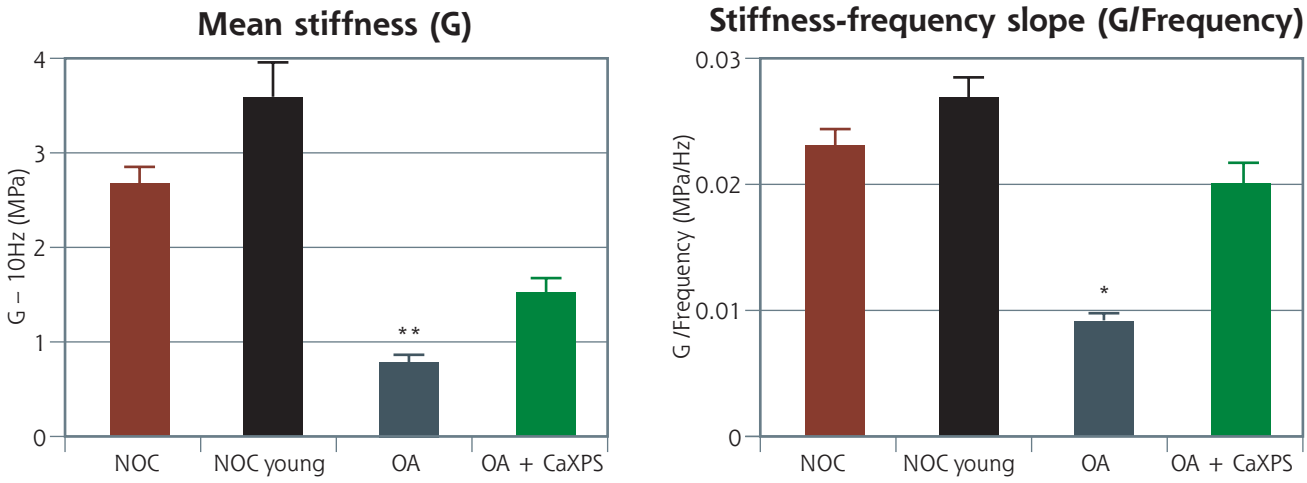



Anabolic (healing) activities – Increased
Mechanical Strength – Increased
Catabolic (degrading) activities – Decreased
Pain and mediators – Decreased
The multiple and beneficial pharmacological activities of CaXPS
Metabolism of connective tissue – Normalised
Circulation, lipids and coagulation – Improved
Pro-inflammatory mediators – Decreased
Immune response – Modulated
Anti-inflammatory mediators – Increased
Inflammation and inflammatory products – Decreased

CaXPS preserves the mechanical properties of cartilage

Prophylactic treatment with 20mg/kg CaXPS orally twice a week for 6 months (OA + CaXPS) maintained the dynamic properties of the tibial articular cartilage (AC) relative to non-treated osteoarthritis (OA) controls in an ovine model of OA. The AC in the central tibial region of the lateral compartment in OA + CaXPS animals showed a thickness, stiffness and stiffness-frequency slope similar to the old non-operated controls (NOC) with values tending towards those of the young NOC. It was suggested that these effects were due to the pro-anabolic and anti-catabolic activities of CaXPS. Appleyard R *et al* (2000), 0320, *46th Annual Meeting Orthopaedic Research Society*, Orlando, Florida, USA.

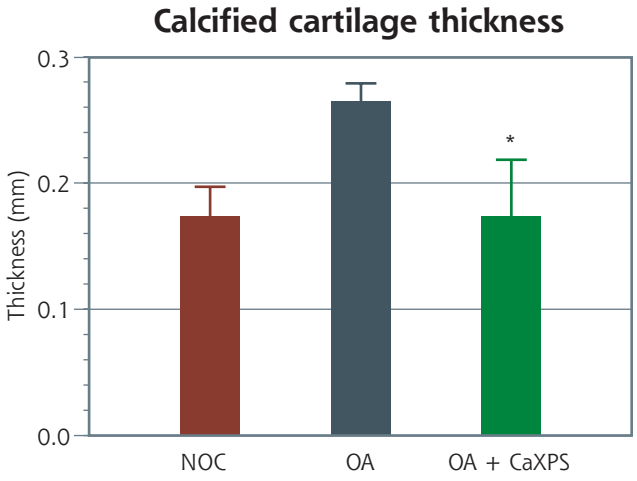
Stiffness data for the lateral-central tibial region AC of non-operated controls old (NOC) and young (NOC young), OA and OA + CaXPS treated animals



* $p < 0.01$, ** $p < 0.0001$

CaXPS protects calcified cartilage

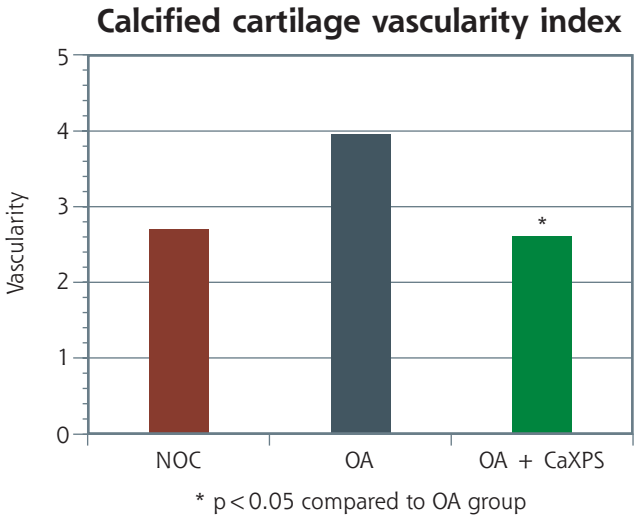
Prophylactic treatment with 20mg/kg CaXPS orally twice a week for 6 months (OA + CaXPS) significantly reduced the thickness of calcified cartilage in the CaXPS treated group compared to the OA group ($p < 0.0001$). Modified Mankin scores (grading of cartilage and subchondral bone for degree of OA) were significantly higher than the non operated controls (NOC) values (OA + CaXPS, $p < 0.02$; OA, $p < 0.007$). Hwa S-Y *et al* (2001) *Osteoarthritis and Cartilage*. 9(Suppl B): S13



* $p < 0.0001$ compared to OA group

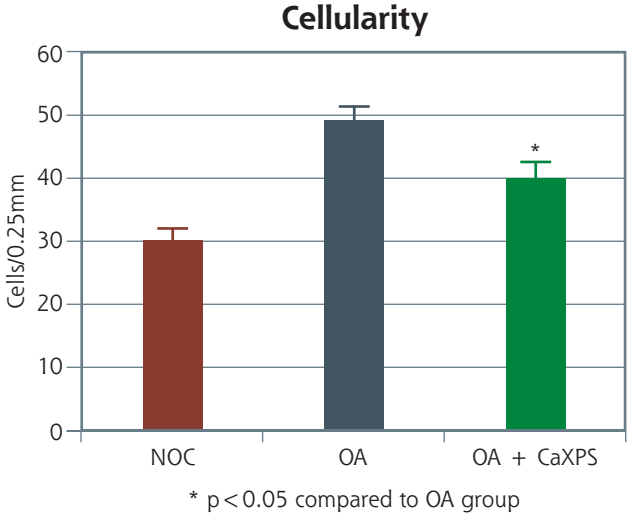
CaXPS protects subchondral bone

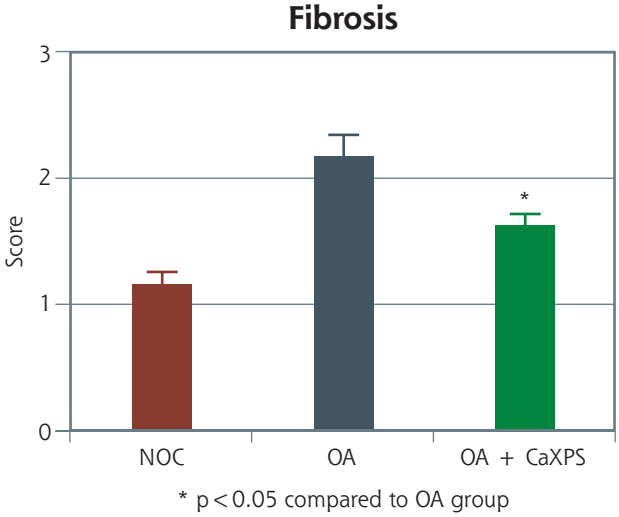
Administration of oral CaXPS at 20mg/kg twice a week for 24 weeks significantly increased the subchondral bone plate thickness ($p < 0.05$), indicating that treated sheep were fully weight-bearing on the meniscectomized joints. The vascularity of the medial femoral condyle and medial tibial plateau of joints in CaXPS treated sheep was significantly decreased compared to the non-treated OA group. Significantly, the uncalcified cartilage did not undergo the hypertrophic changes observed for the untreated OA controls indicating that normal chondrocyte phenotypic expression was maintained by treatment with CaXPS. Hwa *et al* (2002) *Osteoarthritis and Cartilage*. 10(Suppl A): 21



CaXPS decreases synovial inflammatory response

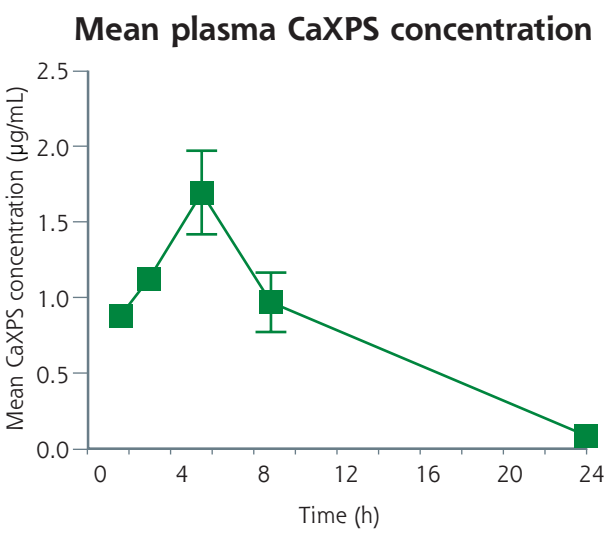
Treatment of sheep with oral CaXPS at 20mg/kg twice a week for 24 weeks increased the biosynthesis of hyaluronan in synovium and reduced the synovial inflammatory response as demonstrated by a significant reduction in subintimal fibrosis and intimal hyperplasia and cellularity ($p < 0.05$). The results of this study support the classification of CaXPS as a Structure Modifying Osteoarthritis Drug (SMOAD). Smith MM *et al.* (2001) *Osteoarthritis and Cartilage.* 9(Suppl B): S4

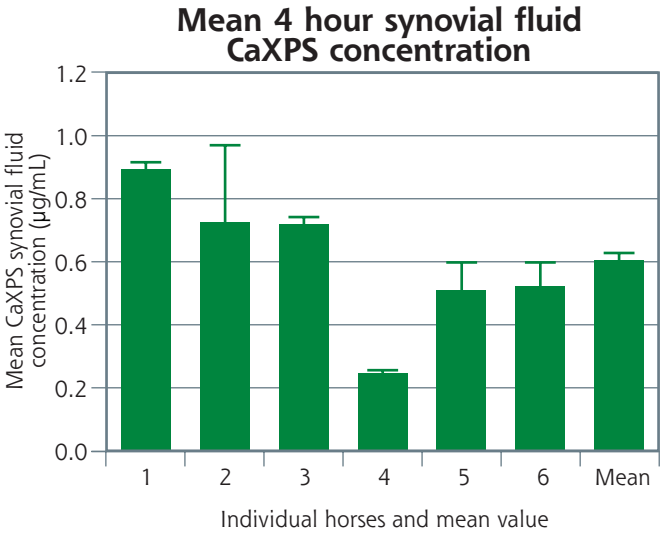




CaXPS achieves biologically active levels in synovial fluid

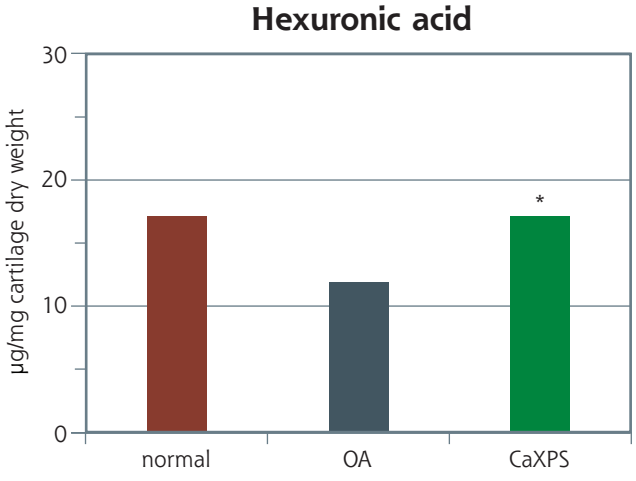
A mean peak CaXPS concentration of 1.7µg/mL (range 0.9–2.8) was achieved 4 hours after a single intramuscular injection of CaXPS at a dose of 2mg/kg. This was associated with a mean synovial fluid concentration of 0.6µg/mL (range 0.2–0.9). This CaXPS concentration in synovial fluid falls within the range reported to stimulate proteoglycan and hyaluronan synthesis by chondrocytes and synovial cells and may also be sufficient to inhibit aggrecanases in cartilage and to increase tissue inhibitor of matrix metalloproteinase-3 tissue levels in the synovial lining and fluid. The synovial fluid levels of CaXPS found in this study may not be maximum as the kinetics of transfer of CaXPS into the equine midcarpal joint are presently unknown and the single 4 hour sampling used may not represent the time when peak values were reached. Fuller *et al* (2002) *Equine Veterinary Journal.* 34(1): 61-64

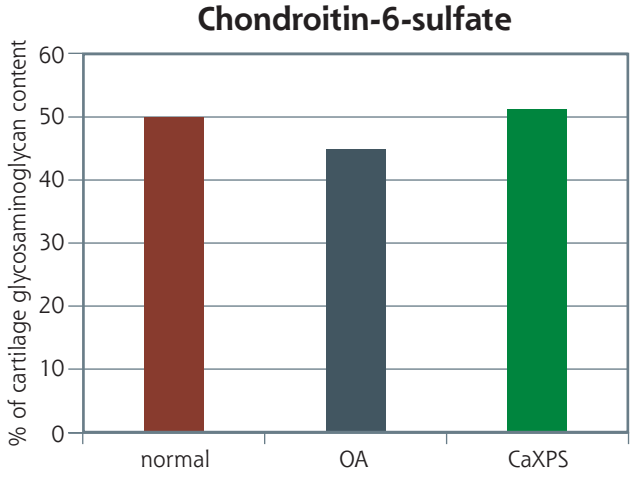




CaXPS preserves cartilage mechanical characteristics

CaXPS (10mg/kg) administered orally maintained the levels of cartilage proteoglycans (PGs) as measured by hexuronic acid content and chondroitin-6-sulphate percentage in knee articular cartilage in a rabbit polycation model of arthritis (day 10). PGs are components of macromolecular aggregates called aggrecans which are important for the functional performance of cartilage. In arthritic cartilage, chondrocyte phenotype changes are shown by an increase in dermatan sulfate (DS) synthesis. CaXPS (10mg/kg) attenuated the production of these small DS containing PG species in cartilage from the arthritic joints (day 10), indicating the preservation of normal biosynthetic activities. Smith MM *et al* (1994) *Arthritis and Rheumatism*. 37: 125-136

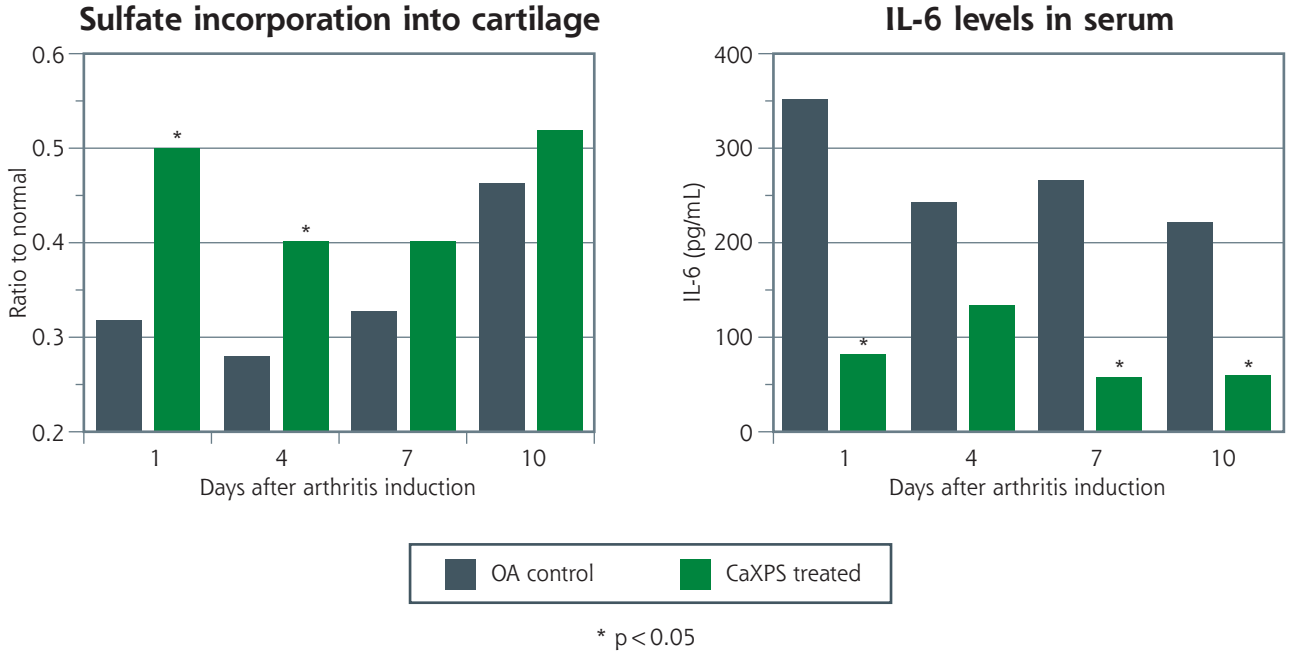




* $p < 0.05$ compared to OA group

CaXPS supports chondrocytes biosynthesis of proteoglycans and lowers serum IL-6

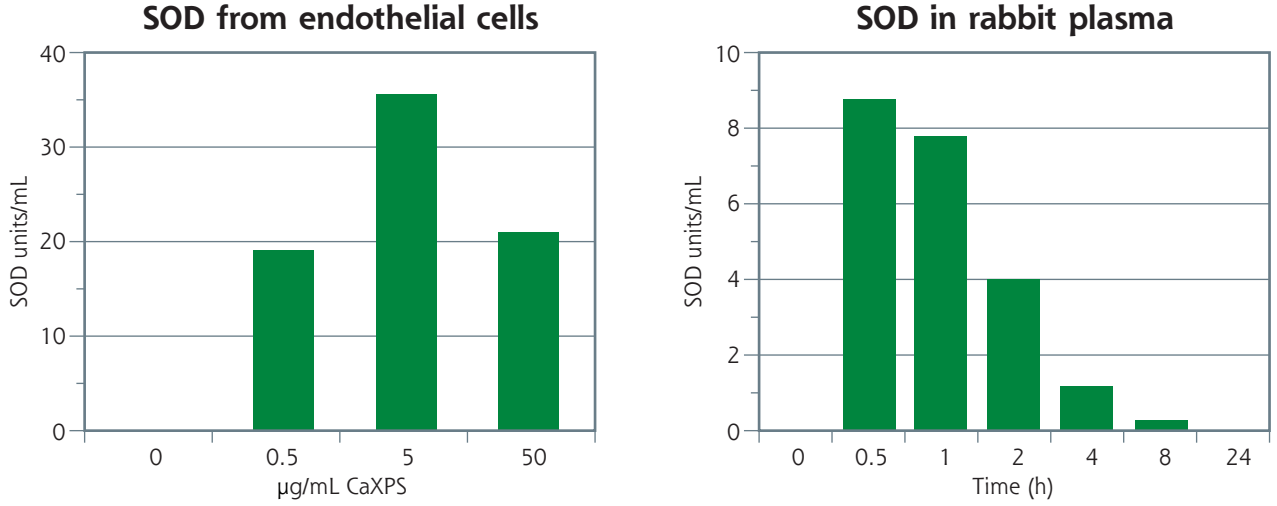
Orally administered CaXPS (10mg/kg) partially reversed the inhibition of newly synthesised proteoglycans (PGs), as measured by radio-sulfate incorporation into cartilage from knee joints of rabbits with experimental arthritis. Serum levels of the inflammatory mediator interleukin-6 (IL-6) correlate with arthritic disease activity and are responsible for the stimulation of release of active phase proteins from the liver. Active phase proteins, such as C-reactive protein, bind tissue breakdown products and stimulate chemotaxis and opsonisation. CaXPS (10mg/kg) reduced the levels of the cytokine IL-6 in the serum of these rabbits by approximately 80% and 70% on days 1 and 10 respectively, reflecting a decrease in release of inflammatory cartilage components. Smith MM *et al* (1994) *Arthritis and Rheumatism.* 37:125-136



* $p < 0.05$

CaXPS stimulates the release of the free radical scavenging enzyme SOD

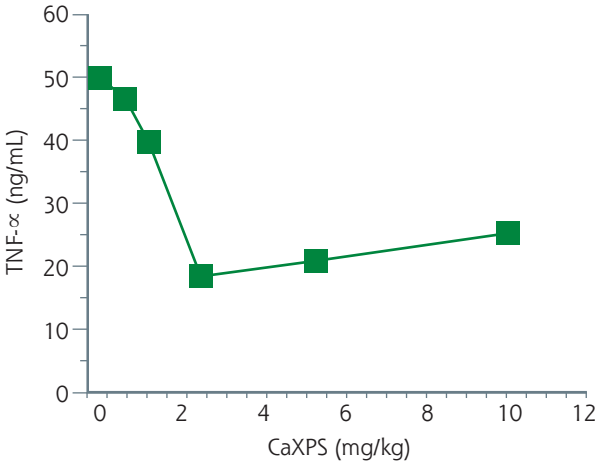
Superoxide dismutase (SOD) is an enzyme which is a potent scavenger of oxygen-derived free radicals that cause damage to tissues. SOD itself has been successfully used to treat arthritis. CaXPS when added to cultured human umbilical endothelial cells, stimulated SOD release. The ability of CaXPS to stimulate SOD release *in-vivo* was confirmed in a study using NZ white rabbits. Maximum SOD levels were found in plasma at 30 minutes after oral treatment at 10mg/kg. These data suggest CaXPS protects connective tissue against free radical damage in the OA joint, thereby preserving normal joint function. Bowman L *et al* (1994) *7th Biennial Meeting International Society for Free Radical Research*, Sydney, Australia.



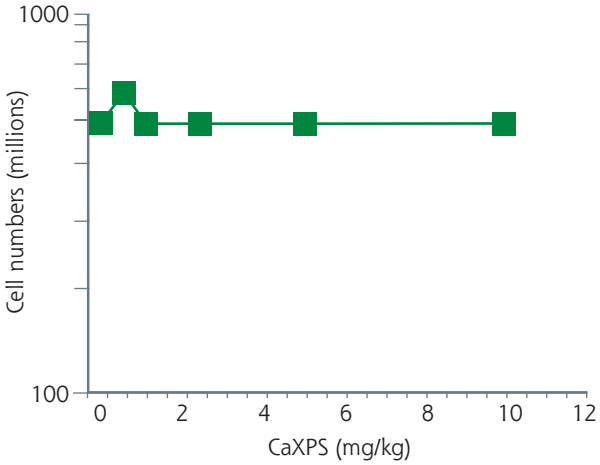
CaXPS decreases the levels of TNF-∝ but has no effect on white blood cell numbers

Tumour necrosis factor (TNF-∝) is a potent mediator of cartilage degradation. It inhibits proteoglycan synthesis by chondrocytes and promotes the release of degradative enzymes and inflammatory prostaglandins by these cells. CaXPS administered subcutaneously reduced TNF-∝ activity in fluids from a rat air-pouch model of joint space inflammation by 38% in the presence of 2.5 to 10mg/kg. CaXPS had no effect on white blood cell numbers in these same fluids. By selectively reducing the destructive effects of TNF-∝ while allowing beneficial cellular activities to be preserved, such as phagocytosis of matrix debris, CaXPS maintains connective tissue structural integrity. Bansal M *et al* (1993) *Current Therapeutic Research.* 54: 714-730

Tumour necrosis factor-∝



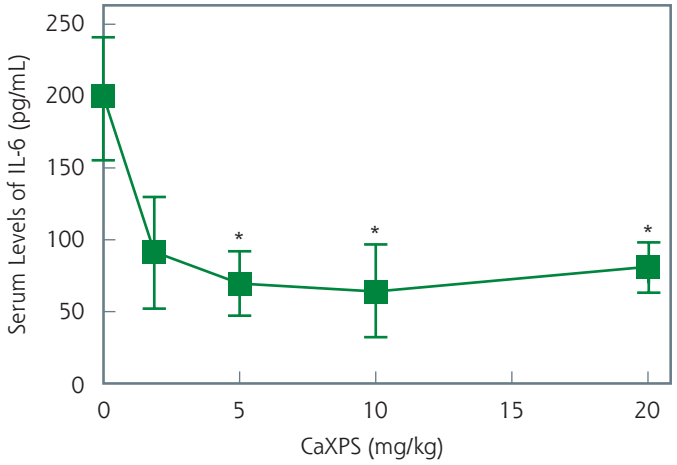
Total white blood cells



CaXPS decreases levels of the pro-inflammatory mediator IL-6

IL-6 is a multifunctional cytokine that is involved in the regulation of acute phase response and activation of T and B cells. The activity of the pro-inflammatory mediator IL-6 was significantly reduced in serum following subcutaneously administered CaXPS doses of 5, 10 and 20mg/kg in the rat. The anti-inflammatory activity of CaXPS was concluded to be a result of its suppressive effects on neutrophil extravasation, activation and production of cytokines and nitric oxide, coupled with its ability to preserve vascular endothelium. Smith M *et al* (1999) *Current Therapeutic Research.* 60(11): 561-576

IL-6 levels in serum

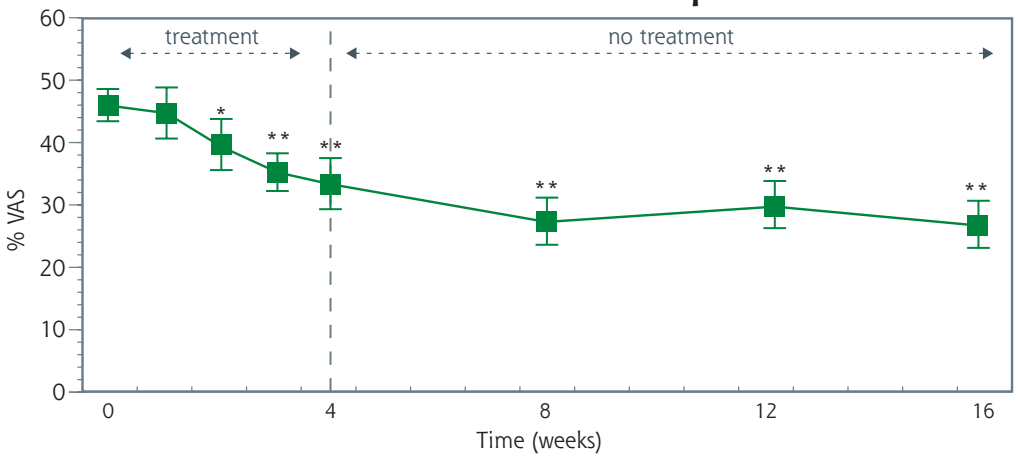


* $p < 0.05$

CaXPS provides relief of pain and improves coagulation and fibrinolysis

A likely cause of the pain of OA is venous congestion in the subchondral bone which may be produced by the increased coagulant activity seen in OA. Five intramuscular injections of CaXPS (2mg/kg once weekly) improved pain scores and functional indices after the third and fourth injections in 23 patients with OA of the knee and finger joints. Coagulant activities were decreased significantly 2 to 4 hours after administration and serum fibrinolytic activity increased significantly 24 hours after administration. Tissue plasminogen activator activity increased after 8 and 24 hours and plasminogen activator inhibitor activity decreased after 4 and 8 hours and continued to decrease 12 weeks after the 5th injection. The patients showed profound changes in serum fibrinolytic activity after administration of the drug, supporting the hypothesis that correction of abnormalities in this system may be responsible for improvement in symptoms. Verbruggen G *et al* (1994) *Osteoarthritis and Cartilage.* 2(Suppl 1):124

The effects of CaXPS on pain

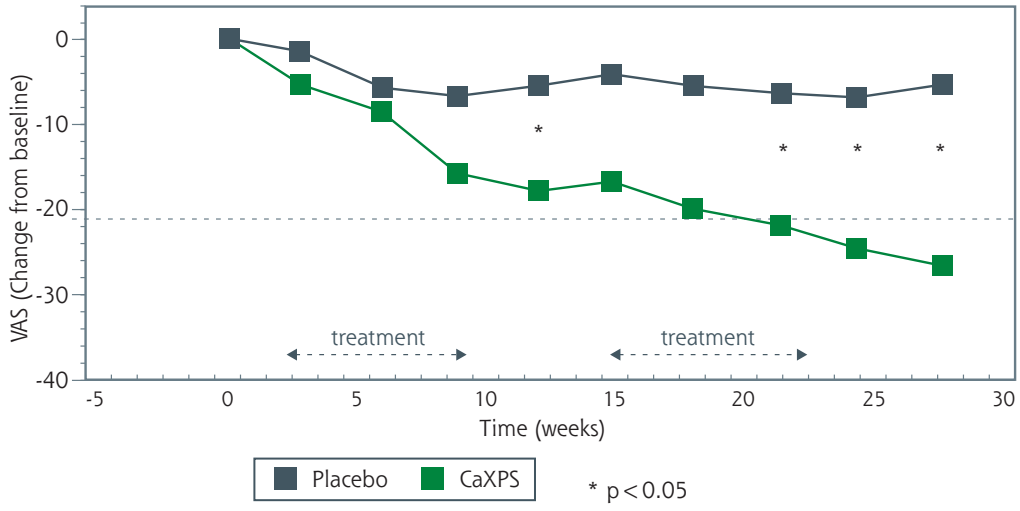


* $p < 0.05$, ** $p < 0.005$

CaXPS treatment results in a significant decrease in night pain

Fifty patients suffering from inflammatory OA of their finger joints were included in a 24 week, double-blinded, randomised, placebo controlled study. Oral CaXPS at 20mg/kg was administered twice a week on an empty stomach during two 6 week periods to 24 patients while placebo was administered in the same way and at the same frequency to 26 patients. Each period was followed by a 6 week wash-out time. Both placebo and CaXPS treated groups showed improvement of most clinical variables after the first treatment period. However, this improvement may have resulted from a placebo-effect as inflammatory episodes of OA of the finger joints are known to resolve spontaneously in many cases. After the second treatment course the placebo group did not show any further change at all, while global pain, morning stiffness, pain at night, dysfunction while conducting 'heavy' and 'light' daily activities, the functional index for finger joints and pain on palpation consistently improved in the CaXPS treated group. It was concluded that the disease/structure modifying properties in OA joint tissues of CaXPS may have caused significant symptom modifying effects in this inflammatory OA condition. Verbruggen G *et al* (1999) *Osteoarthritis and Cartilage*. 7(Suppl A): S37

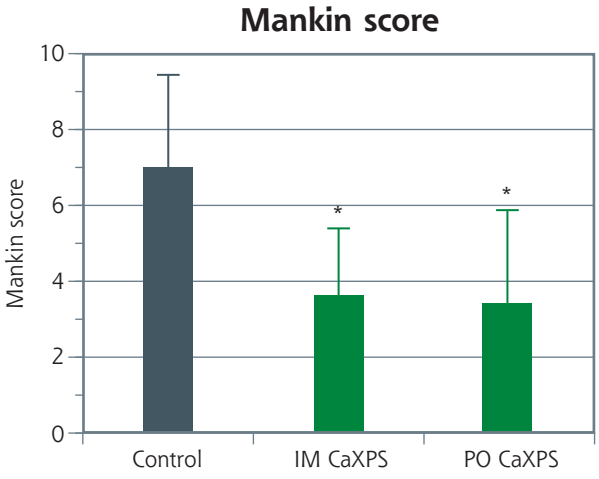
Night pain at rest expressed as change from baseline of mean Visual Analogue Score (VAS) for CaXPS treated and placebo groups



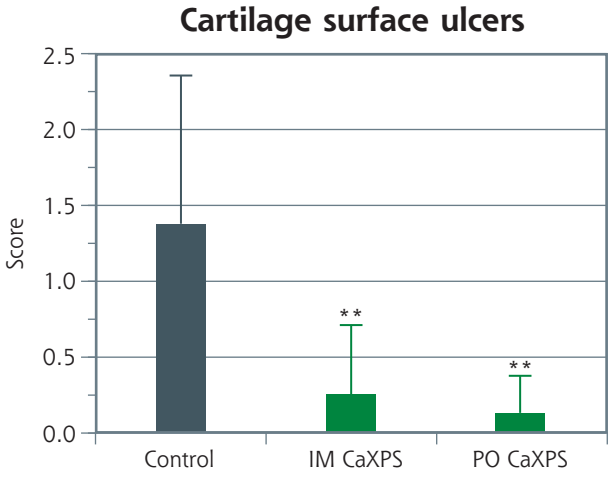
* $p < 0.05$

CaXPS protects cartilage integrity

Fourteen weeks following anterior cruciate ligament (ACL) transection, intramuscular treatment with CaXPS at 3mg/kg weekly for 12 weeks (IM CaXPS) and oral treatment with CaXPS at 10mg/kg twice weekly on an empty stomach for 12 weeks (PO CaXPS), significantly reduced surface ulceration compared to untreated controls. In addition, the Mankin Score (microscopic anatomy of cartilage) was significantly improved in both treatment groups compared to control. Altman RA (1999) *Osteoarthritis and Cartilage.* 7(Suppl A): S18



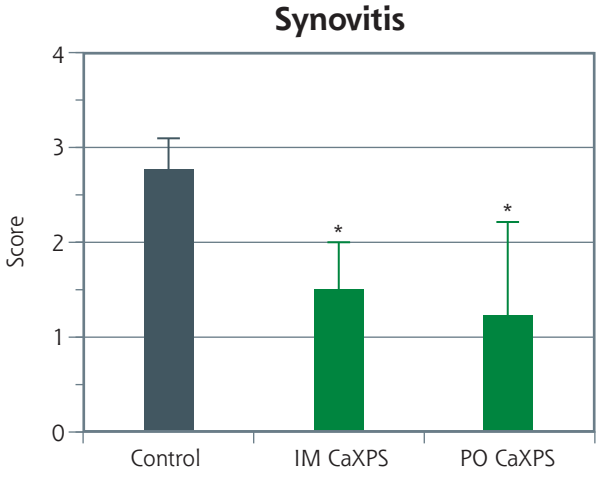
* $p < 0.05$



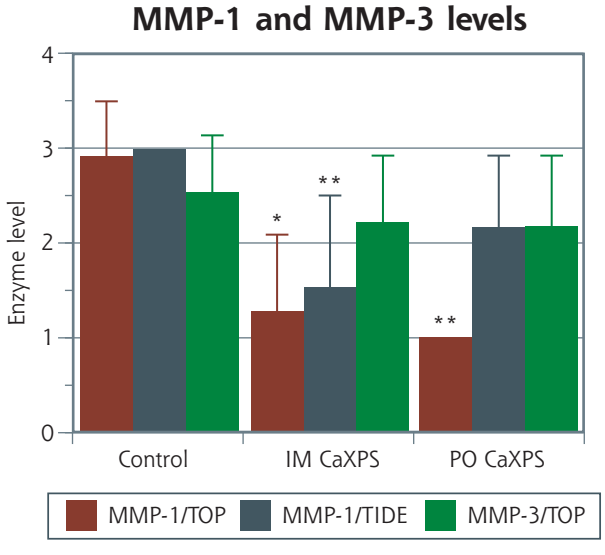
** $p < 0.01$

CaXPS inhibits metalloproteinases and reduces synovitis

In an anterior cruciate ligament (ACL) model, synovitis and synovial fluid volume levels were significantly reduced following intramuscular (IM CaXPS) and oral treatment with CaXPS (PO CaXPS) once a week for 12 weeks at doses of 3mg/kg and 10mg/kg respectively. MMP-1 (collagenase) was reduced in both the surface and tidemark zones in both treatment groups. The surface and tidemark MMP-1 content in the IM CaXPS group was significantly lower than the control ($p = 0.011$ and 0.009 respectively). The mean surface MMP-1 content in the PO CaXPS group was 1.60 which was significantly lower than the control ($p = 0.001$). MMP-1 content in the tidemark zone was not different from the control ($p = 0.077$). MMP-3 (stromelysin) levels in the superficial zone were lower following IM CaXPS and PO CaXPS treatment but were not significantly different from the control group ($p = 0.580$ for both groups). Altman RA (1999) *Osteoarthritis and Cartilage.* 7(Suppl A): S18



* $p < 0.01$

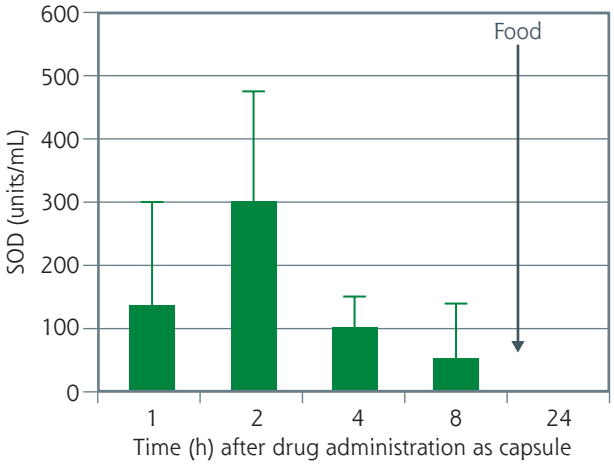


* $p < 0.05$, ** $p < 0.01$

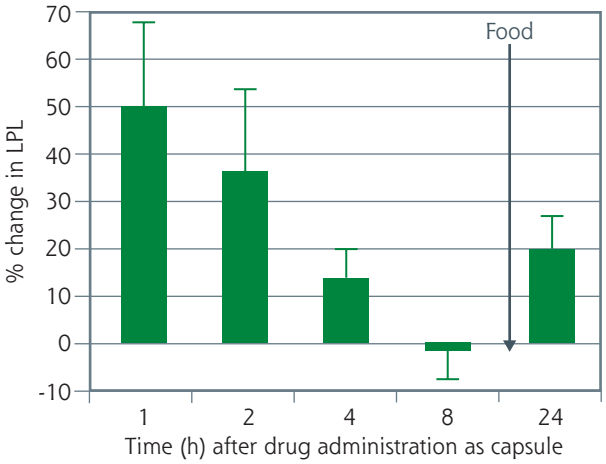
CaXPS stimulates the release of the free radical scavenger protein SOD

Seven fasted adult dogs (15 to 30kg) were given a single oral dose of CaXPS (10mg/kg) as either an aqueous solution (n = 3) or as a formulated capsule (n = 4). Blood was then collected at 0, 1, 2, 4, 8 and 24 hours. Two days later, the groups were switched and CaXPS was administered so that each dog received both formulations. Blood was collected at the same time points. In all drug treated animals, plasma superoxide dismutase (SOD) levels peaked between 2 to 4 hours and lipoprotein lipase (LPL) levels peaked between 1 to 2 hours. There were no statistical differences between the aqueous solution and formulated capsule in their ability to stimulate SOD and lipase release into plasma. These findings support the hypothesis that the ability of CaXPS to mobilise SOD and lipases from endothelial tissues could contribute to the anti-osteoarthritic activity of this drug. Cullis-Hill D *et al* (1995) XIIIth *European Congress of Rheumatology*

Plasma SOD levels



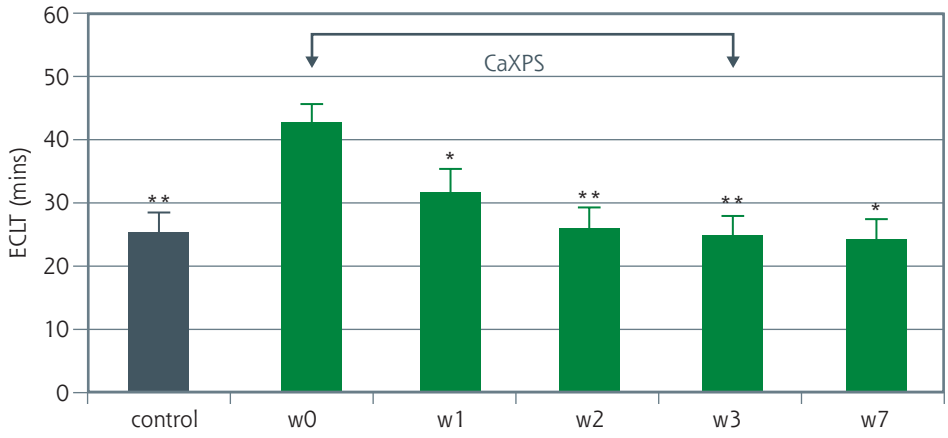
Plasma LPL levels



CaXPS increases fibrinolysis

Twelve large breed dogs with OA were treated with 4 subcutaneous injections of 3mg/kg CaXPS at weekly intervals. A state of hypofibrinolysis was confirmed in the dogs prior to treatment and is consistent with the human OA condition. Following treatment with CaXPS, euglobulin clot lysis time (ECLT), a global measure of fibrinolysis, decreased significantly during the injection period and 4 weeks after the last injection (w7) to levels seen in controls ($p < 0.005$). Ghosh P and Cheras PA (2001) *Best Practice and Research Clinical Rheumatology*. 15(5): 693-710

Rate of Fibrinolysis (ECLT in minutes)

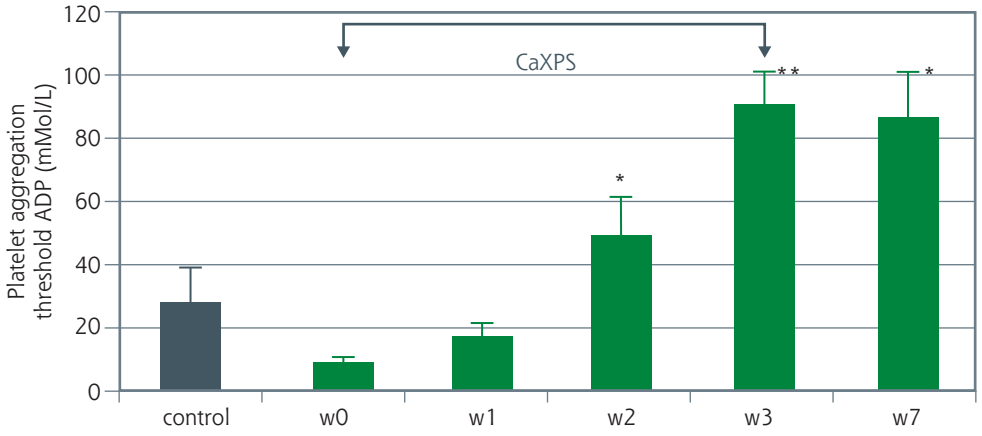


* $p < 0.005$, ** $p < 0.001$ relative to baseline (w0)

CaXPS decreases hypercoagulability

A state of hypercoagulation is known to be associated with the OA process. Platelet aggregability is an indicator of pro-coagulant tendency and can be determined by measuring the platelet aggregation threshold. In a study of 12 large breed dogs with OA, increased platelet aggregability was confirmed prior to treatment. Following 2 subcutaneous injections of 3mg/kg CaXPS at weekly intervals, platelet aggregability had decreased significantly ($p < 0.05$) as shown by the rise in platelet aggregation threshold (w2). This effect was maintained 4 weeks (w7) after the last (fourth) injection (w3). Ghosh P and Cheras PA (2001) *Best Practice and Research Clinical Rheumatology.* 15(5): 693-710

Platelet aggregation threshold

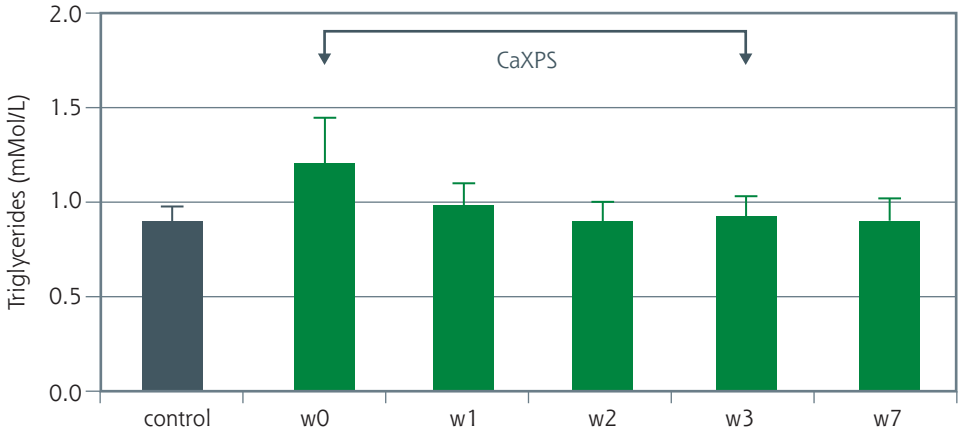


* $p < 0.05$, ** $p < 0.01$ relative to baseline (w0)

CaXPS decreases serum triglyceride levels

It has been proposed that a lipid imbalance is involved in the progression of OA due to impairment of blood flow to joints by embolic lipids and thrombi. Increased cholesterol and triglyceride levels were demonstrated in 12 large breed dogs with OA prior to treatment with 4 subcutaneous injections of 3mg/kg CaXPS at weekly intervals. Following treatment with CaXPS, lipid levels fell to near control levels and these levels were maintained 4 weeks (w7) after the last (fourth) injection (w3). Ghosh P and Cheras PA (2001) *Best Practice and Research Clinical Rheumatology.* 15(5): 693-710

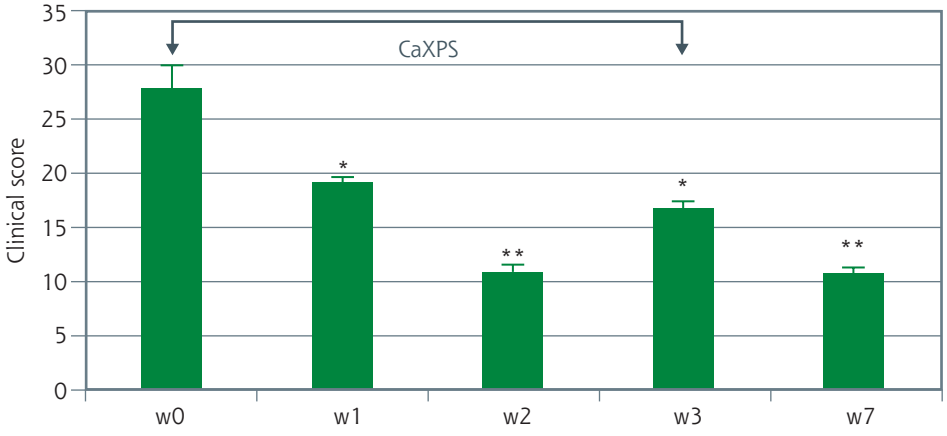
Triglycerides



CaXPS reduces clinical signs in naturally occurring OA

Twelve large breed dogs with OA were assessed for improvements in clinical signs of OA after treatment with 4 subcutaneous injections of 3mg/kg CaXPS at weekly intervals. Assessment of clinical signs was determined using an aggregate clinical score ranging from 0 (no clinical signs) to 100 (most severe). CaXPS treated dogs showed significant improvement from 1 week after the first injection (w1, $p < 0.05$) to 4 weeks after the final injection (w7, $p < 0.005$). Ghosh P and Cheras PA (2001) *Best Practice and Research Clinical Rheumatology,* 15(5):693-710

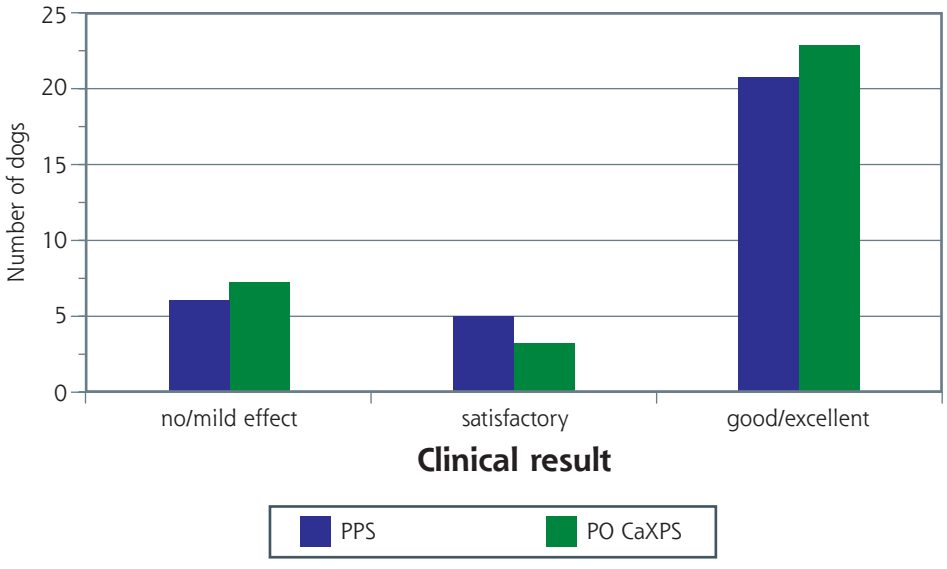
Effects of CaXPS on clinical score in OA



* $p < 0.05$, ** $p < 0.005$ relative to baseline

CaXPS provides equivalent clinical efficacy to injected PPS

Studies of OA dogs have demonstrated that treatment with Sylvet Capsules (PO CaXPS) administered orally at 10mg/kg on 4 occasions at weekly intervals were as effective as treatment with 4 injections of Cartrophen Vet (PPS) at weekly intervals when evaluated for the degree of clinical response assessed by the veterinary surgeon on a 10cm visual analogue scale or 5 point Likert scale. Sylvan Scientific, data on file.



Veterinary and experimental experience shows that various doses can be used

Sylvet Capsules (100mg CaXPS/capsule) when used at dose of 10mg/kg once weekly for 4 weeks is effective as a maintenance clinical dose for the treatment of OA and the associated clinical signs of pain, lameness and stiffness. Veterinary and experimental experience shows that other dosing regimens can help achieve chondroprotective (preservation of articular cartilage) benefits.

Sylvet Capsules are available in 25 and 50 packs

In conclusion, Calcium Xylopyranose Polysulfate (CaXPS) acts in a cascade fashion, regulating joint tissue metabolism through amplification, synergism or down regulation of the different biological systems that affect joint function.

sylvet
capsules

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