Oral Hyaluronan

Oral Hyaluronan Dosage Forms In the Management of Joint Pain

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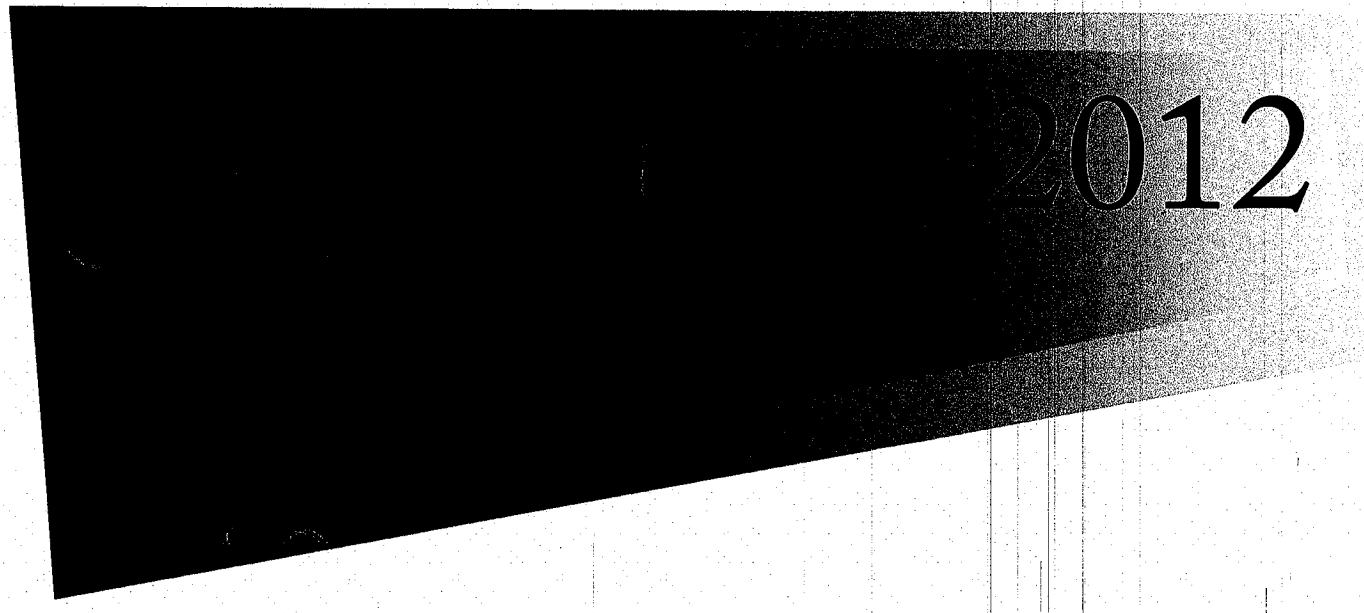

ORAL HYALURONAN DOSAGE FORMS IN THE MANAGEMENT OF JOINT PAIN

Abstract

An evaluation of pain responses specific to joint discomfort was conducted with liquid and tablet oral hyaluronan dosage forms. Participants were randomly assigned in two parallel arms of the open-label clinical trial. Age differences were observed as well as underlying diagnosis and physical parameters, such as weight, activity, and degree of discomfort. Sample size N = 96. Median age was 53.82 years with range from age sixteen to eighty-two years old. Women accounted for 60.4% (n = 58) and men 39.6% (n = 38). Data was collected by self-reporting questionnaires and bio-communication scanning via Zyto technology. Pain parameters were collected via weekly self-directed subjective standardized pain assessment forms. Intake and closeout bio-communication scans were performed to assess objective energy levels in major joints and tissues. Pain response reflected in the analysis of the closeout pain data demonstrated a statistically significant reduction in pain response with the liquid MHB3™. Participants in the liquid group also had significant reduction in discomfort levels progressing through the four-week period. Additionally, the liquid group reported positive effects on range of motion and overall skin health. Conclusion was that liquid MHB3 provided significant relief in overall joint discomfort and provided additive effect of improved range of motion and skin hydration versus tablet form.

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Literature Review

The Research Leading to MHB3® Hyaluronan

ABSTRACT

Numerous studies show that exogenous hyaluronan (also known as hyaluronic acid, sodium hyaluronate, or hyaluronate sodium) can interrupt inflammatory processes and modify the course of disease progression in osteoarthritis and other causes of Chronic Joint Pain. The fundamental basis for these findings lies in the normal role of endogenous hyaluronan in the healthy body. This role can be enhanced by supplying hyaluronan, for example, through viscosupplementation (intra-articular) injection. However, it has recently been demonstrated that an orally administered hyaluronan biopolymer (MHB3 Hyaluronan, Cogent Solutions Group, LLC) can attenuate inflammatory processes, with favorable safety and effectiveness profiles compared to those of injectable formulations. Oral hyaluronan, in particular the highly bioavailable formulation of MHB3 Hyaluronan, is therefore recommended for long-term maintenance of critical joint structures and for ongoing anti-inflammatory prophylaxis.

INTRODUCTION

Treatment of Chronic Joint Pain typically involves the administration of non-steroidal anti-inflammatory drugs (NSAIDs), as well as corticosteroids. However, it is increasingly recognized that the risk profile of such medications does not warrant their use in many circumstances. For this reason, there has been gradual but widespread acceptance of the use of drugs and supplements based on hyaluronan, a natural constituent of joints, having a favorable safety profile. This review highlights basic and clinical research revealing the physiological role of hyaluronan in the maintenance of joint health and the therapeutic role of hyaluronan in the treatment of inflammation, concluding with a summary of the state of current understanding concerning the absorption and distribution of MHB3 Hyaluronan.

HYALURONAN

A ubiquitous constituent of mammalian tissues, hyaluronan, a linear alternating copolymer of D-glucuronic acid β-1,3-D-*N*-acetylglucosamine-β1,4, is particularly abundant in connective tissue. A single hyaluronan molecule can have a molecular weight as great as 8-10 million Daltons (Tammi et al. 2002). **About one-fourth of the hyaluronan in the body is found in the skeleton and joints. Certain specialized tissues and structures, such as synovial fluid, have particularly high concentrations of hyaluronan.** Considerable hyaluronan is carried in lymphatic vessels. Its persistence in plasma is quite limited, with a turnover of between 15 and 35% every minute, since it is removed efficiently and degraded by hepatic endothelial cells (Fraser at al. 1997).

HYALURONAN IN THE HEALTHY JOINT

Hyaluronan, while critical to the function of synovial fluid, is important to other joint structures as well. Articular (hyaline) cartilage in joints contains a large volume of interfibrillar material, including a high concentration of hyaluronan. Hyaluronan serves as the scaffolding to which interfibrillar proteoglycans, especially aggrecan, bind, conferring structural stability to the cartilage. In general, the osmotic pressure created by hydration of the interfibrillar material is opposed by tension in the collagen network (Cohen et al. 1998). Compression forces interfibrillar material out of hyaline cartilage. Osmotic pressure causes the exuded interfibrillar material to move back into hyaline cartilage once the load is removed. **Since hyaline cartilage lacks a blood supply (Suh et al. 1995), hyaluronan-facilitated re-entry is the sole means by which nutrients are carried into hyaline cartilage.**

CHANGES IN HYALURONAN WITH AGING, INJURY OR DISEASE STATES

With aging or osteoarthritis, the superficial collagen network of articular cartilage loses its structural integrity. The interfibrillar component swells as the osmotic pressure created by its hydration is less efficiently opposed by the structurally unsound collagen network. Each cycle of load-bearing thus involves less transfer of fluid out of the cartilage and back in, as the pressure gradient which permits the transfer cycle is diminished (Poole et al. 2002). Concomitant with the changes in the collagen network are changes in hyaluronan. With aging, injury or osteoarthritis, the molecular weight of hyaluronan is decreased. The smaller hyaluronan molecules diffuse more easily in and out of hyaline cartilage and form a less extensive scaffolding to which proteoglycans can bind. As a practical matter, a diminution in the abundance of high molecular weight hyaluronan molecules means that each cycle of load-bearing will involve less fluid turnover and hence less nutrition of the cartilage (Moreland 2003). High molecular weight hyaluronan at joint interfaces normally impedes the flow of fluid, in a phenomenon known as outflow buffering, from the joint cavity into the subsynovial lymphatics. **In osteoarthritis the concentration and the molecular weight of hyaluronan in joints are decreased.** As a result, the hyaluronan less effectively impedes the outflow of fluid from the joint cavity into the subsynovial lymphatic system (Sabaratnam et al. 2005). **This greatly increases the requirement that hyaluronan be replaced.**

HYALURONAN AND THE CONTROL OF JOINT INFLAMMATION

Non-steroidal anti-inflammatory drugs (**NSAIDs**) have been used to control joint pain and improve function but **are associated with gastrointestinal, cardiovascular and renal adverse events, and are not believed to ameliorate the mechanical and metabolic causes of osteoarthritis** (Sarzi-

Puttini et al. 2005). However, an abundance of hyaluronan maintains the long-term structural integrity of the joint cavity. Because these large molecules diffuse only slowly, yet bind large volumes of water, they effectively resist the tendency of compression to force fluid out of the joint and into the general circulation (Coleman et al. 1999). Persistence of hyaluronan in the joint is comparable for endogenous and exogenous hyaluronan (Brown et al. 1991), consistent with favorable results observed in cases of hyaluronan supplementation. Hyaluronan is also directly involved in regulation of the inflammatory response. At sites of inflammation, deposition of hyaluronan, and its complexation with other macromolecules, promotes adhesion of leukocytes rather than their further migration, effectively preventing the leukocytes from receiving more proinflammatory signals in the underlying tissue. The hyaluronan also physically sequesters the proinflammatory mediators, effectively attenuating the inflammatory response (Day and de la Motte 2005). Clinical and experimental work is consistent with the efficacy of hyaluronan in the treatment of certain joint conditions. For example, a recent prospective, randomized, double-blind placebo controlled study evaluated the efficacy of intraarticular hyaluronan for osteoarthritis of the knee. Three weeks post-treatment outcomes were significantly more favorable for the treatment than the control group. However, by weeks 6 and 12 there were no longer any significant differences between the groups (Petrella and Petrella 2006). Recent clinical data are consistent with the notion that **provision of exogenous hyaluronan promotes endogenous hyaluronan production** (Bagga et al. 2006). Exogenous hyaluronan's stimulation of endogenous hyaluronan synthesis stands in contrast to the well-established observation that corticosteroid administration leads to diminished hyaluronan biosynthesis. An abundance of data indicates that **corticosteroids such as hydrocortisone can suppress production of hyaluronan**. In particular, it has been shown that hydrocortisone decreases the expression of *HAS2*, which encodes one of the isoforms of hyaluronan synthase, in response to cytokine stimulation, leading to decreased synthesis of hyaluronan (Jacobson et al. 2000; Wilkinson et al. 2004). It has also been demonstrated that hydrocortisone inhibits the activation of HAS1, another of the hyaluronan synthase isoforms, by interfering with signaling via the p38 mitogen-activated protein kinase pathway (Stuhlmaier and Pollaschek 2004). In addition, methylprednisolone has been shown to cause a decrease in proteoglycan synthesis and an increase in degradation of newly synthesized proteoglycans in cartilage explants (Doyle et al. 2005).

HYALURONAN ABSORPTION AND DISTRIBUTION

MHB3 Hyaluronan is absorbed and distributed to joints. Considerable hyaluronan transport appears to take place via the lymphatics (Liu 2003). A specific receptor for hyaluronan, LYVE-1, was identified on lymph vessel walls (Banerji et al. 1999). Since joint cavities are avascular, all hyaluronan within the joint either is produced locally or arrives by diffusion. Hyaluronan flux from the intestine is stimulated by free fatty acids and bile acids (Reed et al. 1992). Importantly, it has been shown that the molecular weight of hyaluronan found in serum following intravenous administration of a 400,000 dalton formulation is less than that found in serum following oral administration. Vascular inflammatory response was attenuated less effectively by intravenous hyaluronan of 400,000 daltons than by orally administered hyaluronan (Turley and Asculai 2003). MHB3 Hyaluronan **has been shown to be absorbed and effective against important pathophysiological processes, such as inflammation** (Turley 2008). Recent observational clinical studies are consistent with these laboratory findings (Lukens 2005; Kiburz 2006). It has been reported that in racing Quarter Horses intravenous hyaluronan delayed, but only at a statistically insignificant level, the onset of symptoms typically treated by intraarticular injection (McIlwraith et al. 1998). A comparison of intravenous and oral hyaluronan of identical molecular weight range shows that higher molecular weight fragments persist for a longer duration in plasma following oral administration, consistent with the greater observed efficacy of orally administered hyaluronan in decreasing the hallmarks of inflammation (Turley and Asculai 2003). MHB3 Hyaluronan **improves the molecular weight range of circulating hyaluronan by increasing the high molecular weight portion (anti-inflammatory) and decreasing the low molecular weight portion (pro-inflammatory)** (Turley 2008).

SUMMARY

MHB3 Hyaluronan has been shown to be absorbed and bioactive. It can confer a greater and more persistent anti-inflammatory effect than injected hyaluronan. Where occasional injections yield a therapeutic benefit of limited duration, or suppress endogenous hyaluronan production, daily oral hyaluronan supplementation is indicated.

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Evaluation of MHB3® Hyaluronan among Patients with Chronic Joint Symptoms

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Background: One quarter of the American adult population report chronic joint symptoms (CJS). Over 50% of those reporting CJS have symptoms with multiple joints. Among those reporting CJS the joints most effected where the knee (58%), the shoulder (30%), the fingers/thumb (27%), the hip (24%), and the ankle (22%). For this evaluation CJS is defined as joint pain, aching and stiffness during the past 30 days with symptoms onset of over 3 months. Treatment of CJS is usually limited to short-term symptom control with palliative over-the-counter and prescription drugs. Hyaluronan, ubiquitous in body, has multiple complementary mechanisms of action. Hyaluronan directly affects the composition of synovial fluid and provides the backbone for cartilage matrix. Apart from its structural role, hyaluronan influences cell proliferation, differentiation, and migration; angiogenesis, as well as inflammation and immune cell function. Hyaluronan provides a surface to which activated lymphocytes attach attenuating inflammatory response and interrupts chronic substance-P-mediated pain signaling. We assessed the systemic therapeutic effects of a modified oral hyaluronan biopolymer (MHB3 Hyaluronan Cogent Solutions Group, LLC).

Methods: An evaluation of fifty adult subjects (avg. 59 yrs.) with CJS was conducted to identify the effects of daily oral supplementation with MHB3. Subjects self-administered ½ -1 teaspoon of the viscous syrup twice daily for 30 consecutive days. Direct-feedback surveys were completed by participants daily helping facilitate compliance. Subjects identified the affected joints, their pain levels and daily activity levels.

Results: Forty two subjects (84%) reported good to excellent results in relief of pain and stiffness. To be included in the Good to Excellent group the subject had to report a noticeable improvement in joint symptoms with continued relief once the effect was noticed. Four subjects (8%) noticed only minimal benefit during the trial but within 4-5 days of trial termination reported an increase in pain and stiffness, concluding that improvements were gradual and

unremarkable during the trial. This group is not included with the positive results reported above. Four subjects (8%) reported no benefits during the trial. Time to improvement ranged from 5 to 30 days with an average of 21 days. There were no reports of side effects or drug interactions, and no one discontinued the trial. Several subjects voluntarily reduced their Non-Steroidal Anti-Inflammatory Drug (NSAID) use based on improvements during the trial.

Conclusions: Daily supplementation with MHB3® Hyaluronan relieves joint pain and inflammation contributing to an improved range of motion and an increase in daily activity among the majority of subjects with Chronic Joint Symptoms.

Disclosure: Author has nothing to disclose.

Effects of a Modified Hyaluronan Biopolymer (MHB3® Hyaluronan) on Cartilage Loss in a Monoarthritis Model

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Background: Osteoarthritis (OA) is characterized by the progressive loss of articular cartilage. Eventually, in many cases, the entirety of the articular cartilage in certain diarthrodial joints such as the knee, where the femur and tibia articulate, is lost. Frequently compensation for pain results in a loss of range of motion causing an altered gait and the development of OA in other areas.

Commonly used treatments and medications only provide palliative care. Palliative care is defined as any form of medical care or treatment that concentrates on reducing the severity of disease symptoms, rather than halting or delaying progression of the disease or providing a cure. Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are frequently prescribed or self-administered ad libitum. Types include aspirin, ibuprophen, acetaminophen, and naproxen. Although NSAIDs work well for their intended purpose, long-term use of these drugs can cause stomach problems such as ulcers and bleeding. In April 2005 the FDA asked manufacturers of NSAIDs to include a warning label on their product to alert users of an increased risk for cardiovascular events (heart attacks and strokes) and gastrointestinal bleeding. Certain NSAIDs may also weaken bone and increase the risk of bone fractures.

COX-2 inhibitors (coxibs) are also used to treat symptoms. Coxibs block an inflammation-promoting enzyme called COX-2. This class of drugs was initially believed to work as well as traditional NSAIDs, but with fewer stomach problems. However, numerous reports of heart attacks and strokes have prompted the FDA to re-evaluate the risks and benefits of the COX-2s. Rofecoxib (Vioxx) and valdecoxib (Bextra) have been withdrawn from the US market following reports of heart attacks in some patients taking the drugs. Celecoxib (Celebrex) is still available, but labeled with strong warnings and a recommendation that it be prescribed at the lowest possible dose for the shortest duration possible. However, neither

NSAIDs nor COX-2 inhibitors are known to stop or restore the loss of articular cartilage, which is the hallmark of osteoarthritis and the cause of the symptoms.

Steroids and artificial joint fluid (Synvisc, Hyalgan etc.) can be injected directly into the joint capsule to reduce pain and inflammation for up to six months but have attendant injection site risks and do not improve the underlying cartilage condition.

Natural substances marketed in the United States as dietary supplements are also administered in cases of osteoarthritis. In particular, glucosamine, chondroitin sulfate, and methylsulfonylmethane (MSM) are administered in order to provide some relief from the symptoms of osteoarthritis. However, none of these substances is known to address cartilage loss, the root cause of osteoarthritis symptoms.

We constructed a study using an established histopathological scoring system to evaluate specifically the effects of an orally administered, polydisperse, hyaluronan biopolymer (MHB3® Hyaluronan, Cogent Solutions Group LLC) in a mouse model of monoarthritis.

Methods: Thirty 10 week old male C57BL/6 mice purchased from Charles Rivers Laboratories were subjected to a meniscotibial ligament transection surgery of the left knee. This surgery creates a slowly advancing instability condition that mimics the loss of articular cartilage in humans with OA. At week six mice were randomly assigned to 5 groups. Group A (Untreated Controls N6) was euthanized, both left and right knees decalcified, paraffin embedded, stained with Saffrin-O and scored (Pritzker et al.) to confirm disease onset and cartilage loss. A histopathological score of 1 indicates articular cartilage which is intact and pristine. A score of less than 10 indicates that a great deal of healthy articular cartilage remains. A histopathological score of 24 indicates total loss of articular cartilage as is observed in very severe cases. Following confirmation of cartilage loss at week 6 post surgery Group B (Controls, N6) was gavaged 5 days/week for 3 weeks with saline; Group C (Controls, N6) was gavaged 5 days/week for 6 weeks with saline; Group D (Treated, N6) was gavaged 5 days/week for 3 weeks with MHB3 at a dose of 10mg/kg; and Group E (Treated, N6) was gavaged 5 days/week for 6 weeks with MHB3 at a dose of 10mg/kg. At the end of week 9 Groups B and D were euthanized, their left and right knees scored and compared. At the end of week 12 Groups C and E were euthanized, their left and right knees scored, and compared.

Results: The average scores in Group A (untreated week 6 baseline) were: left knee 5.33/24; right knee 1.80/24 confirming disease onset. The average scores in Group B (week 9 saline control) were: left knee 10.70/24; right knee 4.17/24. The average scores in Group C (week 12 saline control) were: left knee 12.80/24; right knee 3.40. The average scores of Group D (week 9 MHB3® Hyaluronan treated) were: left knee 7.25/24; right knee 2.0/24. The average scores of Group E (week 12 MHB3 Hyaluronan treated) were: left knee 7.84/24; right knee 1.08/24.

Conclusion: The results of this study strongly support the disease modifying and chondroprotective benefits of the oral hyaluronan biopolymer MHB3 Hyaluronan when used in an established model of osteoarthritis. This is the first time that an orally administered, exogenous hyaluronan biopolymer has been shown to have such benefits.

Figure 1. Group A Untreated Control Left Knee Average Score 5.33/24 Week 6

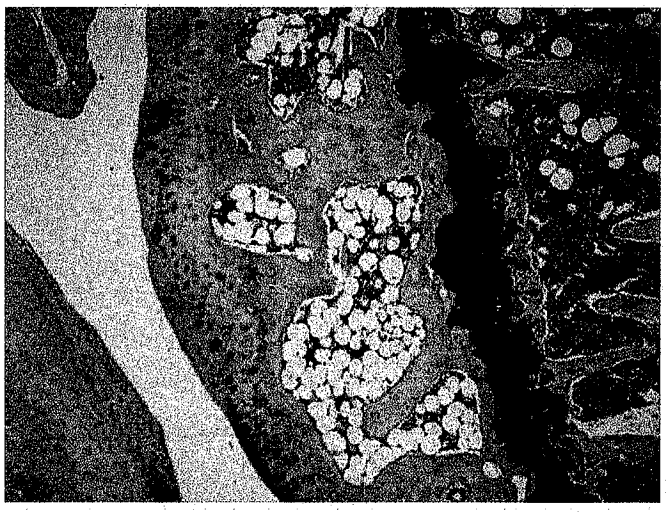


Figure 2. Group A Untreated Control Right Knee Average Score 1.80/24 Week 6

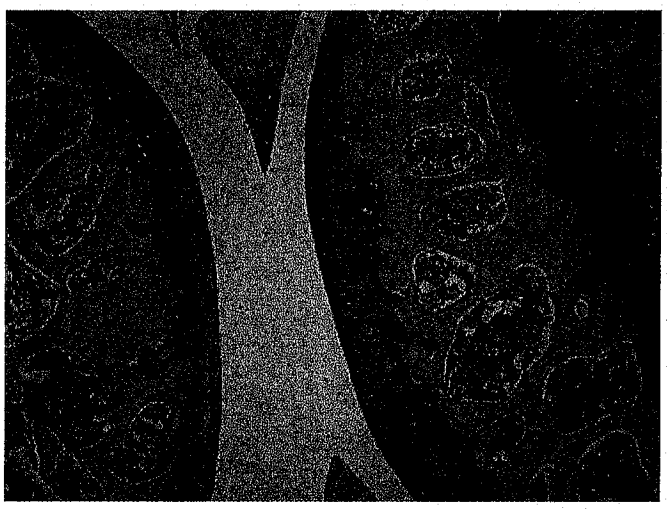


Figure 3. Group B Saline Control Left Knee Average Score 10.7/24 Week 9

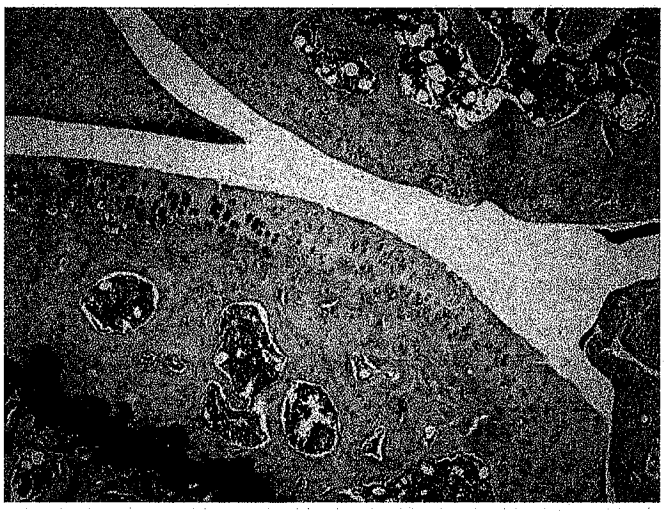


Figure 4. Group B Saline Control Right Knee Average Score 4.17/24 Week 9

Figure 5. Group C Saline Control Left Knee Average Score 12.8/24 Week 12

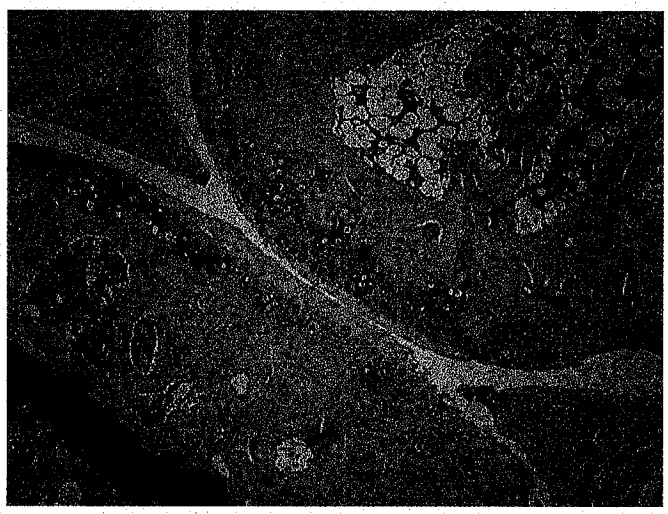


Figure 6. Group C Saline Control Right Knee Average Score 3.40 Week 12

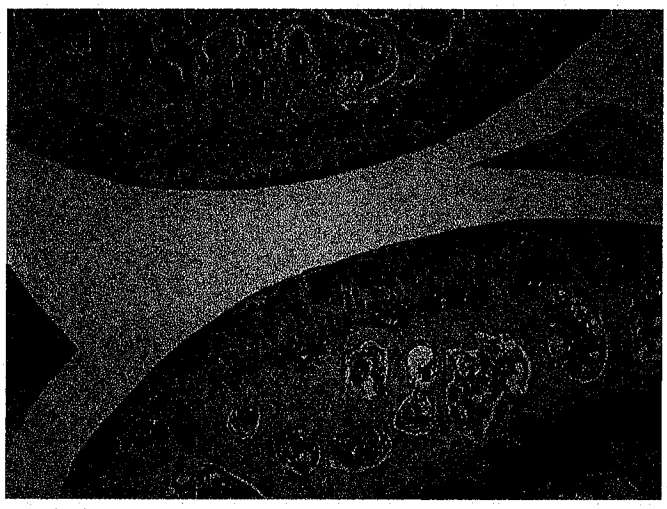


Figure 7. Group D MHB3® Treated Left Knee Average Score 7.25/24 Week 9

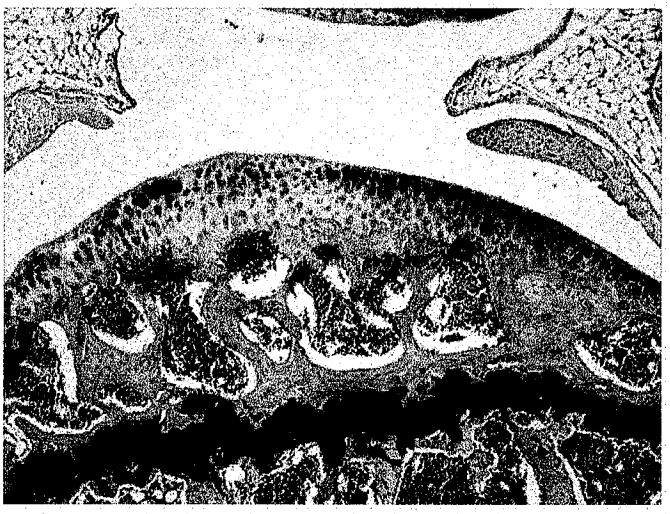


Figure 8. Group D MHB3® Treated Right Knee Average Score 2.00/24 Week 9

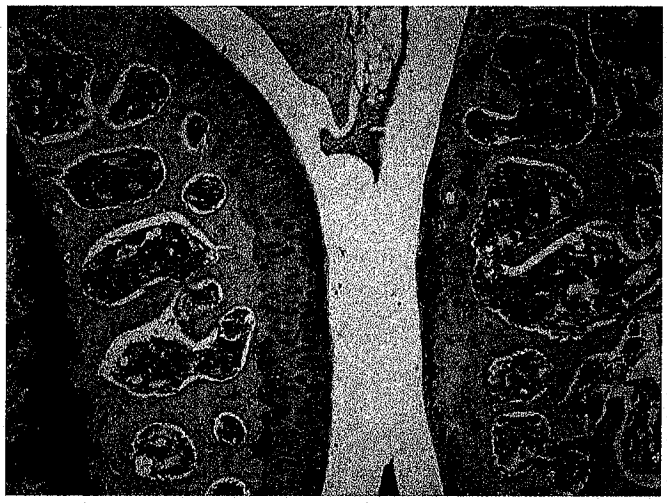


Figure 9. Group E MHB3 Treated Left Knee Average Score 7.84/24 Week 12

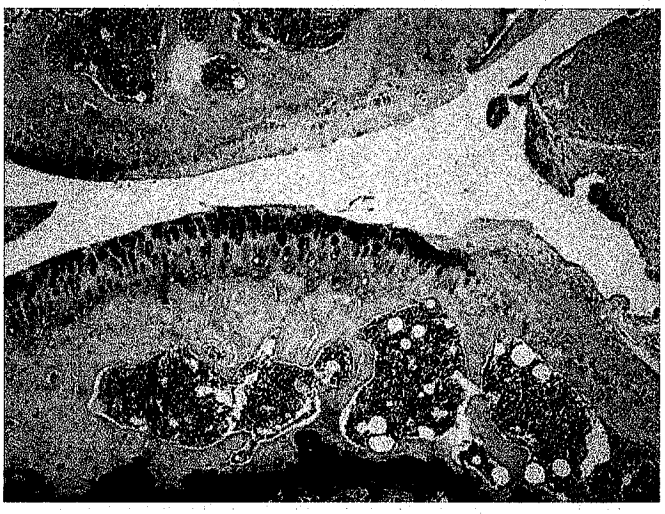
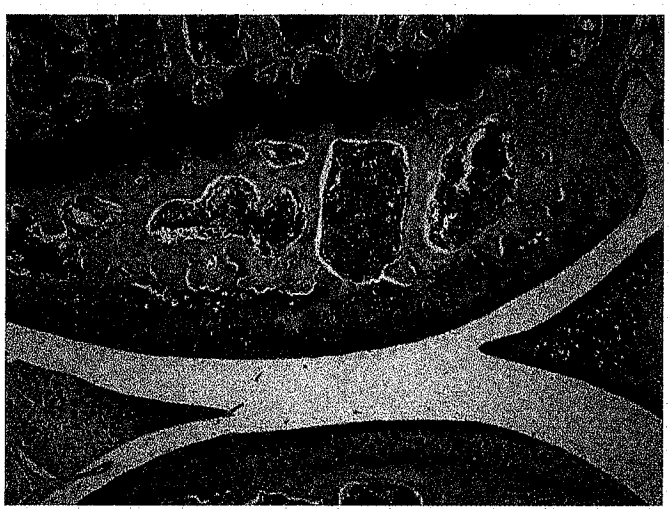


Figure 10. Group MHB3 Treated Right Knee Average Score 1.08/24 Week 12



Evaluation of a Modified Hyaluronan Biopolymer (MHB3® Hyaluronan) on Cartilage Loss and Osteophyte Formation in a Knee Instability Model

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Background: Osteophytes, commonly called bone spurs, are bony projections that develop along the edges of bones accompanying cartilage loss. They may form on any bone including vertebrae, and often form where bones meet at joints. Osteophytes may also develop where ligaments and tendons connect to bone. Range of motion is frequently limited in the affected joint and although osteophytes themselves are not painful, they frequently rub against nerves and cause pain. All vertebrate species are subject to the development of osteophytes.

Osteophyte formation has been classically related to any sequential and consequential changes in bone formation due to aging, degeneration, mechanical instability, and osteoarthritis. For Forty two percent of the adult human population, degeneration and development of osteophytes will lead to symptoms of neck and back pain, radiating arm and leg pain and weakness in the extremities during their lifetime.

Medical treatments for cartilage loss and osteophytes are typically palliative and not directed at the underlying problem. Osteophytes that limit range of motion or cause other problems that limit ability may require surgery to prevent further joint damage. Surgical options are determined by the location of the osteophyte. Osteophytes are often removed as part of a more comprehensive surgery for osteoarthritis. For example with osteoarthritis in an elbow the surgeon may remove osteophytes while making other repairs to the joint. Access to the joint for removal of osteophytes may be via arthroscopic surgery or with an open procedure.

A study was designed and conducted to examine the effect of an orally administered exogenous hyaluronan biopolymer (MHB3® Hyaluronan, Cogent Solutions Group) on cartilage loss, bone remodeling and osteophyte development.

Methods: A total of 10 inbred laboratory mice were obtained and housed according to accepted laboratory animal standards. The mice underwent an aggressive knee instability surgery. The medial collateral and anterior cruciate ligaments were identified and transected followed by a partial meniscectomy. Following surgery mice were randomly assigned to two groups. Control Group (N5) was gavaged 5 days/week for 4 weeks with saline. Treatment Group (N5) was gavaged 5 days/week with MHB3 Hyaluronan at a dose of 10mg/kg, for five weeks. During the five weeks post-surgery, it was anticipated that all animals would have severe cartilage loss, bone remodeling and osteophyte development. After five weeks of treatment the mice were euthanized, their knees decalcified, paraffin embedded, stained with Saffrin-O, evaluated on slides (Figure 1) and scored on a scale of 1 to 24 (Pritzker *et al).* A histopathological score of 1 indicates pristine articular cartilage such as might be found in a very young healthy subject; a score of 24 indicates complete cartilage loss, poor bone reformation, and likely osteophyte formation.

Results: All of the control mice showed complete cartilage denudation and the formation of osteophytes scoring 24/24 at the effected joint. The treatment group averaged scores of 5/24 showing significant healthy cartilage and no osteophyte formation.

Disscussion: As shown in Figure 1 Control Mouse (left), the red-staining tissue with poorly defined margins on the interior of the bone tissue is indicative of a failed attempt to remodel the bone and the formation of osteophytes leading to severe instability. On the other hand, the sample Treatment Mouse (right), which was orally administered the hyaluronan composition exhibits well-defined bright red-staining tissue on the surface of the bone. The well-defined margins of red-staining tissue are indicative of intake and healthy cartilage and bone surfaces.

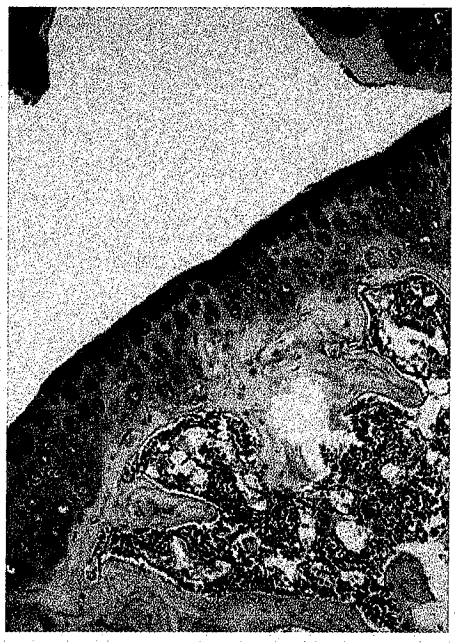
Conclusions: These results strongly demonstrate the effectiveness of the oral administration of MHB3® Hyaluronan in protecting healthy cartilage and bone, and the prevention of osteophytes in mice having undergone knee instability surgery, as compared to those mice receiving a saline control composition. This is the first time, to our knowledge, that an orally administered, exogenous hyaluronan biopolymer has been shown to have cartilage and bone protecting benefits including osteophyte prevention.

FIGURE 1

Saline Control Group Sample

Sagittal section of knee joint post-MCL/ACL resection showing loss of articular cartilage, poor bone remodeling, and formation of osteophytes.

MHB3 Treated Group Sample



Sagittal section of knee joint post-MCL/ACL resection showing healthy articular cartilage with no indication of poor bone remodeling or osteophyte formation.

Evaluation of MHB3® Hyaluronan on the Development of Osteopenia

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Background: Osteopenia is a common bone loss condition preceding frank osteoporosis, and is often associated with estrogen depletion. N-terminal collagen peptides in serum are increased with osteopenia. Elisa analysis of elevated collagen peptide levels using monoclonal antibodies to detect the peptides is used clinically to measure response to bone building medications and is an accepted measure of osteopenia. Endogenous hyaluronan (HA) with particular molecular characteristics is now considered to play a role in the regulation of bone physiology. The effects of oral MHB3 Hyaluronan supplementation on bone loss were investigated in an established model of osteopenia using ovariectomized (OVX) female rats.

Methods: Female Sprague Dawley rats (N=25) were purchased from Charles River Laboratories. Three (3) rats served as untreated weight controls. Seventeen (17) rats received bilateral OVX and were randomized into 2 groups. The OVX placebo (PBS) group (N=5) was gavaged with physiological saline 5 days/week, the OVX treatment group (N=12) was gavaged with 1.0 mg MHB3/kg 5 days/week. Five (5) rats received sham surgeries and were gavaged 1 x PBS 5days/week. Blood (0.3 ml) was drawn from rats' tail veins 3 days prior to commencing gavage and at D26 and D54. Blood was centrifuged and the resulting sera was immediately stored at –20°C. Peptide levels were measured using a competitive-inhibition enzyme-linked immunosorbent assay for qualifying serum collagen N-terminal peptides (Osteomark NTx kit). Assays were performed according to the manufacturer's instructions.

Results: No animals were lost during the study and no clinical signs of morbidity were observed. By D14, PBS OVX animals had gained significantly more weight than PBS Sham animals. MHB3® Hyaluronan treated animals exhibited the same weight gain as PBS control animals. Serum collagen levels in PBS sham, PBS OVX, and MHB3 OVX animals were analyzed at D26 and D54. Serum collagen peptide levels at D26 were similar in all three groups suggesting that significant bone loss had not yet occurred. However by D54 serum collagen peptide levels had significantly increased in PBS OVX animals compared to PBS sham. Micro-CT scans confirmed that significant bone loss had occurred at this time. MHB3 OVX animals also exhibited serum peptide levels that were significantly less than PBS-OVX animals suggesting a protective effect of MHB3 in osteopenia.

Conclusion: MHB3® Hyaluronan administered 5 days/week by oral gavage significantly reduces the development of osteopenia associated with estrogen depletion, as detected by levels of N-terminal collagen peptides in serum.

Disclosures: Authors have no disclosures to declare.