

Double Blind Placebo Controlled Study Confirms Rapid 10-Day Results Seen in Previous Human Trials:

Natural Eggshell Membrane (NEM®) is a Natural Therapeutic Choice for Joint & Connective Tissue Disorders



Abstract

Introduction: Natural Eggshell Membrane (NEM®) is a new novel dietary supplement that contains naturally occurring glycosaminoglycans and proteins essential for maintaining healthy joint and connective tissues. Two single center, open label pilot clinical studies were conducted to evaluate the efficacy and safety of NEM® as a treatment for pain and inflexibility associated with joint and connective tissue disorders. The follow-up randomized, multicenter, double blind, placebo controlled Osteoarthritis Pain Treatment Incorporating NEM® (OPTION) clinical study was conducted to evaluate the efficacy and safety of NEM® as a treatment for pain and stiffness associated with osteoarthritis of the knee.

Methods: Patients received oral NEM®, 500 mg once daily, for four weeks (open label) or eight weeks (placebo controlled). The primary outcome measure for the open label trials was to evaluate the change in general pain associated with the treatment joints/areas at 7 and 30 days. In the Single-Arm Pilot Trial, range of motion (ROM) and related ROM-associated pain was also evaluated. The primary endpoint for the OPTION trial was the change in overall Western Ontario and McMasters Universities (WOMAC) Osteoarthritis Index, as well as pain, stiffness, and function WOMAC subscales measured at 10, 30, and 60 days.

Results: Single-Arm Pilot Trial: Supplementation with NEM® produced a significant treatment response at 7 days for flexibility (27.8% increase) and at 30 days for general pain (72.5% reduction), flexibility (43.7% increase), and ROM-associated pain (75.9% reduction). Double-Arm Pilot Trial: Supplementation with NEM® produced a significant treatment response for pain at 7 days for both treatment arms (X: 18.4% reduction, Y: 31.3% reduction). The significant treatment response continued through 30 days for pain (30.2% reduction). Placebo Controlled OPTION Trial: Supplementation with NEM® produced an absolute rate of response that was statistically significant (up to 26.6%) versus placebo at all time points for both pain and stiffness, and trended toward improvement for function and overall WOMAC scores. Rapid responses were seen for mean pain subscores (15.9% reduction) and mean stiffness subscores (12.8% reduction) occurring after only 10 days of supplementation. At 60 days, pain response was maintained (15.4%), while stiffness had improved further to 26.6% reduction. Mean function subscores showed a 15.5% absolute improvement versus placebo at 10 days, which fell slightly to 13.5% by day 60. Overall mean WOMAC scores resulted in a 15.2% absolute improvement versus placebo at 10 days, which was maintained at 60 days (15.1%). There were no serious adverse events reported during any of the studies and the treatment was reported to be extremely well tolerated by study participants.

Conclusions: Natural Eggshell Membrane (NEM®) is a possible new effective and safe therapeutic option for the treatment of pain and inflexibility associated with joint and connective tissue (JCT) disorders, particularly osteoarthritis (OA). Supplementation with NEM®, 500 mg taken once daily, significantly reduced pain and stiffness, both rapidly (7-10 days) and continuously (60 days). It also showed clinically meaningful results from a brief responder analysis, demonstrating that significant proportions of treated patients will be helped considerably with NEM® supplementation. Subjects taking NEM® did not report any gastric or cardiac side effects associated with long-term use of other JCT or OA treatments, such as NSAIDs. The Clinical Trial Registration numbers for these trials are: NCT00750230, NCT00750854, and NCT00750477.

Growing Need for Joint Supplements

It is estimated that 140 million adults in the United States suffer from some form of joint or connective tissue (JCT) disorder (i.e. arthritis, lupus, gout, fibromyalgia, neck or back pain, etc.) with arthritis being the most prevalent (1; 2). Osteoarthritis (OA) is by far the most common form of arthritis and is estimated to affect nearly 27 million adults in the U.S., with one third of those 65 and older having been diagnosed with OA (2). As the population ages, this estimate is expected to grow rapidly. Traditional treatments for most of these disorders attempt to address only the symptoms (pain, inflammation, and discomfort) associated with the diseases. Most of these treatments have shown limited effectiveness in randomized controlled clinical trials (RCTs) (3; 4; 5; 6) or are known to have significant and sometimes severe side effects. To avoid the cardiac risks (7; 8), gastrointestinal issues (9; 10), and dependency issues (11; 12) associated with traditional treatments (particularly with long-term use), many patients have turned to complementary and alternative medicines (CAMs) such as dietary supplements. Because of the limited effectiveness of dietary supplements glucosamine and chondroitin alone, the search for additional CAMs to treat OA continues.

Discovery of Eggshell Membrane

Other vitamins, minerals, and botanicals such as methylsulfonylmethane (MSM), *S*-adenosylmethionine (SAME), kava, pine bark extract, capsicum, boswellia root extract, turmeric/curcumin, etc. are also marketed for various JCT pain maladies. We present here the use of eggshell membrane as a possible new natural therapeutic for JCT disorders. In the U.S. alone, an estimated 600,000 tons of eggshells are produced annually as a by-product of the poultry industry (13). Disposal of these eggshells creates an environmental and financial burden and, therefore, alternative uses for these materials would be of obvious benefit. Eggshell membrane is primarily composed of fibrous proteins such as Collagen Type I (14). However, eggshell membranes have also been shown to contain glycosaminoglycans, such as dermatan sulfate and chondroitin sulfate (15), sulfated glycoproteins including

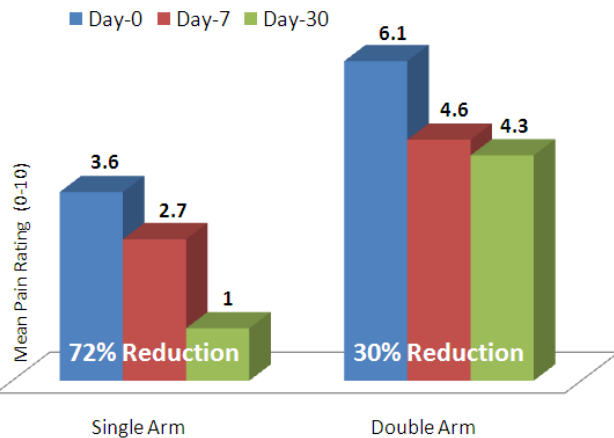
hexosamines, such as glucosamine (16), hyaluronic acid (17), and sialic acid (18). The discovery of eggshell membrane as a natural source of combined collagen, glucosamine, chondroitin, and hyaluronic acid has prompted the evaluation of this material as a potential treatment for joint and connective tissue pain. ESM Technologies, LLC (Carthage, MO) has developed methods to efficiently and effectively separate eggshell membrane from eggshells to create an essentially shell-free eggshell membrane. The isolated membrane is then partially hydrolyzed using a proprietary process and dry-blended to produce 100% pure Natural Eggshell Membrane (NEM[®]). Compositional analysis of NEM[®] conducted by ESM has identified a high content of protein and moderate quantities of glucosamine, chondroitin sulfate, hyaluronic acid, and collagen (primarily Type I).

Clinical Trials

Joint and connective tissue disorders are extremely common in the United States and result in significant costs, both financial and quality-of-life, for those that suffer from the debilitating diseases. These human clinical trials were designed to evaluate the efficacy and safety of Natural Eggshell Membrane as a treatment option for JCT disorders, particularly osteoarthritis. Results from these studies indeed indicate that NEM[®] is both effective and safe for treating pain associated with JCT disorders and considerably improves flexibility and reduces stiffness in the affected joints/areas. NEM[®] has the added benefit of avoiding the concerning side effects associated with long-term use of other JCT treatments, such as narcotics or NSAIDs.

Single-Arm & Double-Arm Pilot Trials: Patients experienced relatively rapid (7 days) responses for pain (Double-Arm) with a mean response of approximately 25% (X: 18.4% & Y: 31.3%) and flexibility (Single-Arm) with a mean response of approximately 28%. By the end of the follow-up period (30 days) the mean response for pain had improved to 30% (Double-Arm) and 73% (Single-Arm). At the same time, flexibility improved to a mean response of approximately 44% and the ROM-associated pain had a mean response of approximately 76% (Single-Arm). A brief responder

Effect of NEM® on Joint Pain In Open-label Clinical Trials



Single Arm Trial

Approx. 1/3 of patients experienced >30% reduction in pain @ 7 Days.

Approx. 1/3 of patients experienced >50% reduction in pain @ 30 Days.

Double Arm Trial

Approx. 2/3 of patients experienced >50% reduction in pain @ 30 Days.

Approx. 1/2 of patients reported that they were Pain-Free @ 30 Days.

Approx. 1/2 of patients experienced >50% improvement in flexibility @ 30 Days.

analysis of the data provides a number of clinically relevant highlights. In both the Single-Arm Pilot Trial and the Double-Arm Pilot Trial, a significant proportion of the study populations (64% & 35%, respectively) experienced a greater than 50% reduction in pain by 30 days. Of particular note is that nearly half (45%) of the patients in the Single-Arm Pilot Trial reported that they were pain-free (reported a score of zero) by 30 days of supplementation. All patients in the Single-Arm Pilot Trial experienced at least some improvement in flexibility or ROM-associated pain, with more than half (55%) of the subjects experiencing a greater than 50% improvement in flexibility and more than one-third

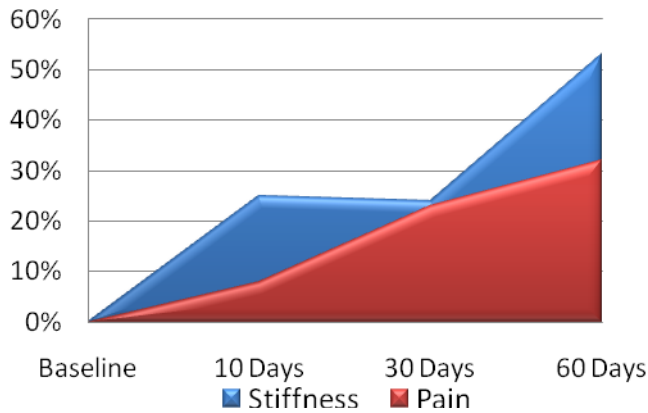
(36%) of the subjects reporting that they were pain free during ROM evaluation.

Placebo-controlled OPTION Trial: Patients experienced a relatively rapid (10 days) response for all WOMAC scores with a mean response of approximately 15% (12.8% to 15.9%). By the end of the follow-up period (60 days) the mean response remained approximately 15% (13.5% to 15.4%) for all WOMAC scores except stiffness which was 26.6%. This is superior to the response shown for glucosamine and chondroitin in previous clinical investigations (19; 20).

Again, a brief responder analysis of the data provides a number of clinically relevant highlights. It becomes evident that there are response rates that are quite likely to be clinically relevant ($\geq 30\%$ reduction from baseline), as well as response rates that are most assuredly clinically relevant ($\geq 50\%$ reduction from baseline). For example, approximately one-third (33%) of study subjects experienced greater than 30% reduction in pain at 10 days, with a similar number of subjects (32%) having experienced greater than 50% reduction in pain at 60 days. In both instances, this rate was more than two times ($\sim 2.5x$) that of the placebo group. Approximately one-quarter (25%) of study subjects experienced greater than 50% reduction in stiffness at 10 days, with the number of patients increasing to more than one-half (53%) having experienced greater than 50% reduction in stiffness at 60 days. The 10-day result was more than two times ($\sim 2.5x$) that of the placebo group and the 60-day result was nearly five times ($\sim 4.8x$) that of placebo.

Performing a Number Needed to Treat (NNT) analysis of the OPTION data provides further clinically relevant information. By 30 and 60 days, NNTs for at least 50% reduction in pain were 5.6 and 5.0, respectively. In clinical practice, one out of every five patients should experience at least a 50% reduction in pain within 30-60 days. By comparison, we determined an NNT of 23.8 from the GAIT data (glucosamine & chondroitin trial) for a 50% reduction in WOMAC pain scores for the overall study population (19). A similar 50% reduction in rheumatoid arthritis pain was reported as an NNT of 4 in a review of three clinical trials for

Percent of NEM[®] Treated Patients Experiencing >50% Improvement.



- ✓ One-third of patients experienced >30% reduction in Pain @ 10 Days.
- ✓ Nearly one-third of patients experienced >50% reduction in Pain @ 60 Days.
- ✓ One-fourth of patients experienced >50% reduction in Stiffness @ 10 Days.
- ✓ More than half of patients experienced >50% reduction in Stiffness @ 60 Days.

adalimumab, etanercept, and double-dose infliximab (21). Similarly, results can be found for painful diabetic neuropathy in which NNTs range from 3.6 to 6.2 for 50% pain relief (22). Although the last two examples are not direct comparisons to OA pain treatment, they serve to demonstrate clinically effective treatment NNT values for pain-associated conditions.

NNT values were also determined for 50% reduction in stiffness at each time point. We obtained NNTs of 6.5, 7.9, and 2.4 at 10, 30, & 60 days, respectively. This demonstrates that there is a clinically relevant reduction in stiffness at all time points during the study. This is particularly true at 60 days where nearly one out of every two patients would experience a 50% reduction in stiffness.

NEM[®] is almost 5X more clinically effective than Glucosamine or Chondroitin (alone or in combination)*

Number Needed to Treat Pain Comparison for NEM[®]

NEM [®] NNT (> 50%) Pain	Other NNTs (> 50%) Pain
5.0 60 days	23.8 (Glucosamine / Chondroitin) 6 months
	14.9 (celecoxib) 13 weeks
	4.0 (adalimumab, etanercept, & double-dose infliximab) 12 months

Number Needed to Treat (NNT): the number of patients needed to treat to see a clinically significant treatment effect versus placebo.

*NNT for glucosamine & chondroitin calculated from the GAIT Study (*N Engl J Med* 2006, 345(8):795-808.)

The safety profile for NEM[®] is also of significance as there are no known side effects, excluding the obvious egg allergy concern. This is of obvious importance in a condition that requires long-term treatment such as JCT disorders. Significant and sometimes serious side effects associated with other treatments can force patients to have to make the difficult decision between living with the disease symptoms or living with the side effect symptoms.

Conclusion

With so many people suffering from joint and connective tissue disorders, and that number expected to grow immensely as the overall U.S. population ages, it is important for patients to have treatment options that are both effective and safe. The reporting of the results from these three human clinical trials demonstrates that Natural Eggshell Membrane (NEM[®]) is a viable treatment option for the management of JCT disorders.

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