PRODUCT FOCUS

Natural Eggshell Membrane (NEM®)

A novel dietary supplement for joints health

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Chronic inflammatory complaints of joints and connective tissues are highly incident in western countries and frequently cause severe disability: arthritis, lupus, gout, fibromyalgia and other pathologies fall into this broad definition, with osteoarthritis being the most prevalent. Epidemiological data support the hypothesis that by 2020 arthritis will affect sixty million Americans and limiting almost twelve millions in their normal daily activity. The incidence increases as population ages but, unfortunately, safe and effective pharmacological tools are still lacking to fight most of these ailments. Some are auto-immunes and may benefit from immune-suppressant drugs but, more often, therapy is primarily targeted at obtaining symptomatic control. Non Steroidal Anti-Inflammatory Drugs (both un-selective and selective COX-2 inhibitors) and corticosteroids are used in the managing of flogosis and pain. They can be administered alone or combined with analgesics of variable potency, including opioids. The chronic and degenerative course, coupled with severe side effects of the available drugs, makes the long-term therapy of joints and connective tissue diseases somehow puzzling. Patients frequently apply to complementary and alternative treatments, by themselves or under the supervision of physicians. Glucosamine and chondroitin sulphate, alone and combined together, have long been proposed as *nutraceuticals* to improve pain and stiffness associated with osteoarthritis; their efficacy is however questionable, since two well designed clinical trials demonstrated either null or modest improvement on the WOMAC (Western Ontario and McMasters Universities) scale, an international index for clinical evaluation of knee and hip osteoarthritis. Furthermore, the EFSA panel recently rejected health claims proposed for these two ingredients under article 13.1 (general function health claims) not recognizing a cause-effect link between the supplementation of glucosamine and/or chondroitin sulphate and the maintenance of healthy joints. Besides these two compounds, vitamins and minerals (ascorbic acid, tocopherol, B-complex, zinc, copper and selenium), *botanicals* (Boswellia serrata, Curcuma longa, pine bark, Capsicum annuum and Salix alba) and other *nutraceuticals* (omega-3, Methyl Sulphonyl Methane and S-adenosylmethyonine) are proposed and marketed as nutritional aids for osteoarthritis and related diseases.

Pilot clinical studies have prompted Natural Eggshell Membrane (NEM®) as a promising new dietary supplement potentially effective in reducing pain and stiffness associated to osteoarthritis. ESM Technologies (Carthage, MO, USA) developed a gentle, eco-compatible method to isolate membranes from the chicken eggshell and obtain NEM® in the form of partially hydrolyzed powdered product.

Chicken eggshell consists of the calcified external part and of the attached membranes (one inner and one outer) whose main biological functions are retaining the embryo before calcium deposition, providing a proper surface area for this process and preventing microbial contaminations. Eggshell membranes might also actively participate to egg's development releasing some growth factors. Since recent years eggshell has been considered just an industrial by-product but compositional analysis showed it could be a valuable source of biologically active compounds. Eggshell membranes contain fibrous proteins (type I, V and X collagen), glycosaminoglycans (hyaluronic acid, dermatan sulphate and chondroitin sulphate), glucosamine, low but significant percentages of uronic and sialic acid, enzymes (such as lysyl oxidase, ovotransferrin and lysozyme). A batch of NEM® is typically composed of 0.5-1 percent hyaluronic acid, 0.2-0.5 percent chondroitin sulphate, 12-18 percent collagen, 45-50 percent proteins and appears as an off-white powder.

Taking into account such analytical data, two pilot open-label clinical studies investigated the feasibility of NEM® as a nutritional alternative for alleviating pain and stiffness in osteoarthritis patients. 10 subjects with persistent, mild to moderate pain (minimum level 2 on the 0-10 Likert scale) caused by joint and connective tissue pathologies were randomized to receive once-daily 500 mg NEM® capsules (single-arm study) after stopping analgesic medications and after a wash-out period. The primary outcome measured was patient's self-evaluation of general pain on the Likert-analogue scale in comparison to pre-treatment levels; results were recorded at day 7 and 30. Secondary outcomes were joints flexibility measured by means of the Range of Motion (ROM) test and the pain felt during its execution; before starting the treatment, mean values of these three parameters were calculated.

NEM® administration improved flexibility (+ 27,8 percent, P = 0.038) at day-7, while general pain (- 72.5 percent, P = 0.007) and ROM test-associated pain (75.9 percent, P = 0.007) both improved at day-30. Pain reduction failed to achieve significance at day-7 because of statistical disproportionation; patient compliance and treatment tolerability were high.

Another open-label study (double-arm) evaluated the effectiveness of two NEM® formulations which differed in degree of hydrolysis: Y-arm formulation was 2, 5 fold more hydrolyzed than the X-arm formulation. Dosage and duration were the same as in the single-arm trial, with general pain being the only endpoint evaluated.

A total of 28 subjects were enrolled but one in each arm leaved during the treatment and two in the X-arm didn't start it at all. Despite the high drop-out, results were consistent with those of the single-arm trial: a fast reduction (X = - 18.4 percent, P = 0.021; Y = - 31.3 percent, P = 0.014) in general pain was recorded after day-7 for both arms. Since the difference was considered not clinically relevant, subjects enrolled in the Y arm joined the X-arm for the rest of the treatment. Improvement persisted at day-30, with a mean reduction in general pain of 30.2 percent (P = 0.0001) and NEM® supplementation again showed high tolerability and optimal compliance.

The significance of data collected from these studies was scarce, due to clear design limitations (no placebo, low number of subjects enrolled and inhomogeneity of clinical conditions including differences in sites involved and types of complaints).

However, it emerged a good potential for NEM® as an alternative therapy in osteoarthritis needing more scientifically sound demonstration. Trying to accomplish this goal a double-blind, randomized, placebo-controlled, multicenter trial (OPTIC, Osteoarthritis Pain Treatment Incorporating NEM® Clinical study) was designed, whose results were disclosed in a 2009 issue of *Clinical Rheumatology*.

67 patients from three rheumatology clinics in USA were enrolled, representing the intent-to-treat population of the study. 29 out of them were randomized to assume once-daily 500 mg NEM® capsule and 31 a placebo capsule; at the end of the trial an overall 43 percent drop out was recorded probably, authors think, due to the strict requirements in rescue management of pain (only acetaminophen allowed).

Eligibility criteria were: grade I-III osteoarthritis of the knee with a minimum score of 30 mm on WOMAC Visual Analogue Scale 100 mm, a psychometric evaluation tool for pain. Among main exclusion criteria there were immune-suppressant therapies in the past 3 months, presence of inflammatory diseases other than osteoarthritis mimicking knee pain and known allergies to egg and its components. A proper washout period was established for previous drugs and nutritional supplements such as methyl sulphonyl methane, glucosamine and chondroitin sulphate (3 months).

Primary endpoints were considered improvements, versus placebo, in overall WOMAC score and in pain, stiffness and function of the knee sub-scores; secondarily, tolerability and compliance to NEM® were evaluated. Results were recorded at day 10, 30 and 60 after starting the treatment. Taken together, a reduction in pain and stiffness (from 10,30 to 26.6 percent) emerged for experimental versus placebo group at day-10: mean sub-scores were - 15.9 percent (P = 0.036) for pain and - 12.8 percent (P = 0.024) for stiffness, the first remaining constant until the day-60, the latter increasing to - 26.6 percent (P = 0.005). Variations in joints function and overall WOMAC score lacked significance although improving by an absolute 8.8 percent (function, day-30) to 15.5 percent (function, day-10) and by 9.6 percent (overall WOMAC, day-30) to 15.2 percent (overall WOMAC, day-30).

Although the statistical significance of results is affected by an high drop out percentage and the small number of subjects enrolled, this trial did put NEM® under a spotlight confirming its positive action in osteoarthritis is more than putative and also definitively demonstrating it's safe, well tolerated and allows high compliance due to once-daily dosage not applicable to other supplements (i.e. glucosamine and chondroitin sulphate) and the majority of drugs. Authors considered clinically relevant that one-third of subjects on NEM® reported more than 30 percent reduction in knee pain at day-10 and one-fourth more than 50 percent reduction in stiffness at the same time point. In the experimental group at the end of the trial (day-60) improvements in pain were maintained and those in stiffness were extended to more than a half of subjects.

Of course, these data need to be strenghten by larger clinical trials and even more stratified to better establish which types of osteoarthritis patients are good candidates to a successfull NEM® supplementation. Mechanism of action should also be elucidated from a pharmaco-dynamic point of view; one preliminary research on rats (data not yet disclosed) indicates that oral administration of NEM® may inhibit some pro-inflammatory cytokines and other factors involved in the acute phase response, modulating flogosis and pain.

REFERENCES AND NOTES

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