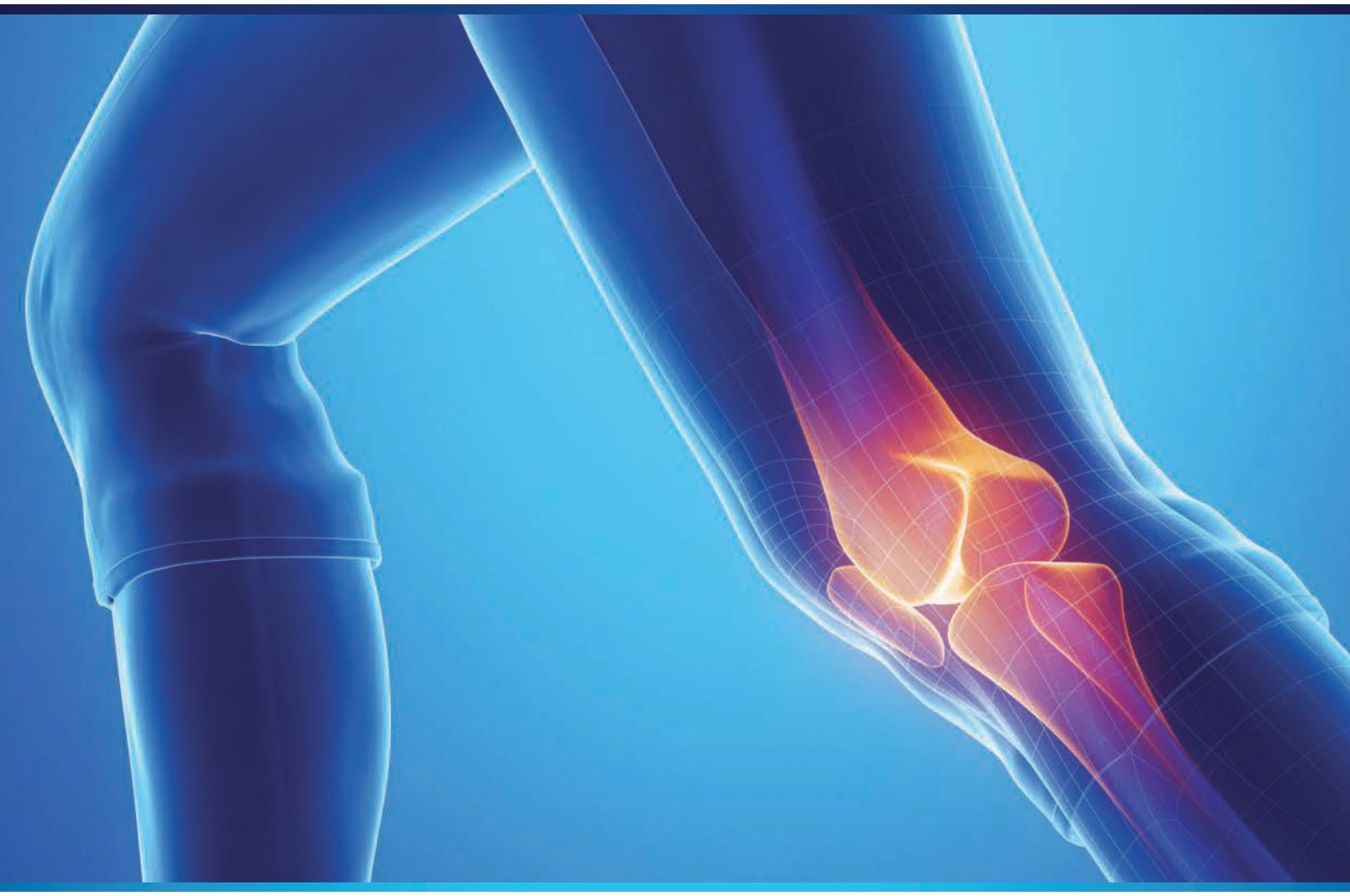


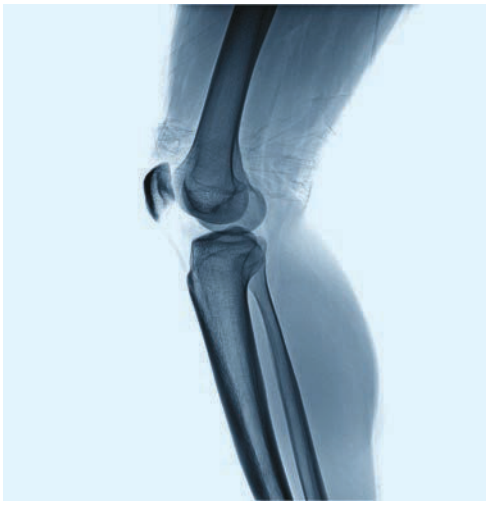
Aquamin

& Osteoarthritis

Summary

Aquamin is a natural ingredient for the enhancement of joint health. It contains significant quantities of calcium and magnesium as well as trace amounts of 72 additional minerals complexed together in a structure engineered by the cell wall of the seaweed Lithothamnion Sp. Aquamin has been the subject of 33 peer reviewed publications over the last 10 years, which support its unique health promoting properties. Aquamin has been shown to improve mobility and reduce the pain and stiffness associated with osteoarthritis. This paper details the studies undertaken thus far in the area of joint health.

Osteoarthritis | Overview



Osteoarthritis (OA) is a common and progressive joint disorder, which mostly affects adults and is characterised by joint degeneration resulting in extreme pain, disability, and reduced quality of life. The most commonly affected joints include those in the hands, neck, lower back and weight-bearing joints such as the knees and hip. OA affects over 250 million people worldwide, imposing a substantial burden on society [1]. OA ranks as the fifth highest cause of years lost to disability in the whole population in high-income countries, and the ninth highest cause in low- and middle-income countries. It accounts for 50% of the entire musculoskeletal disease burden, and thus is considered the highest-burden condition within the musculoskeletal group of diseases, which also includes rheumatoid arthritis and osteoporosis [2].

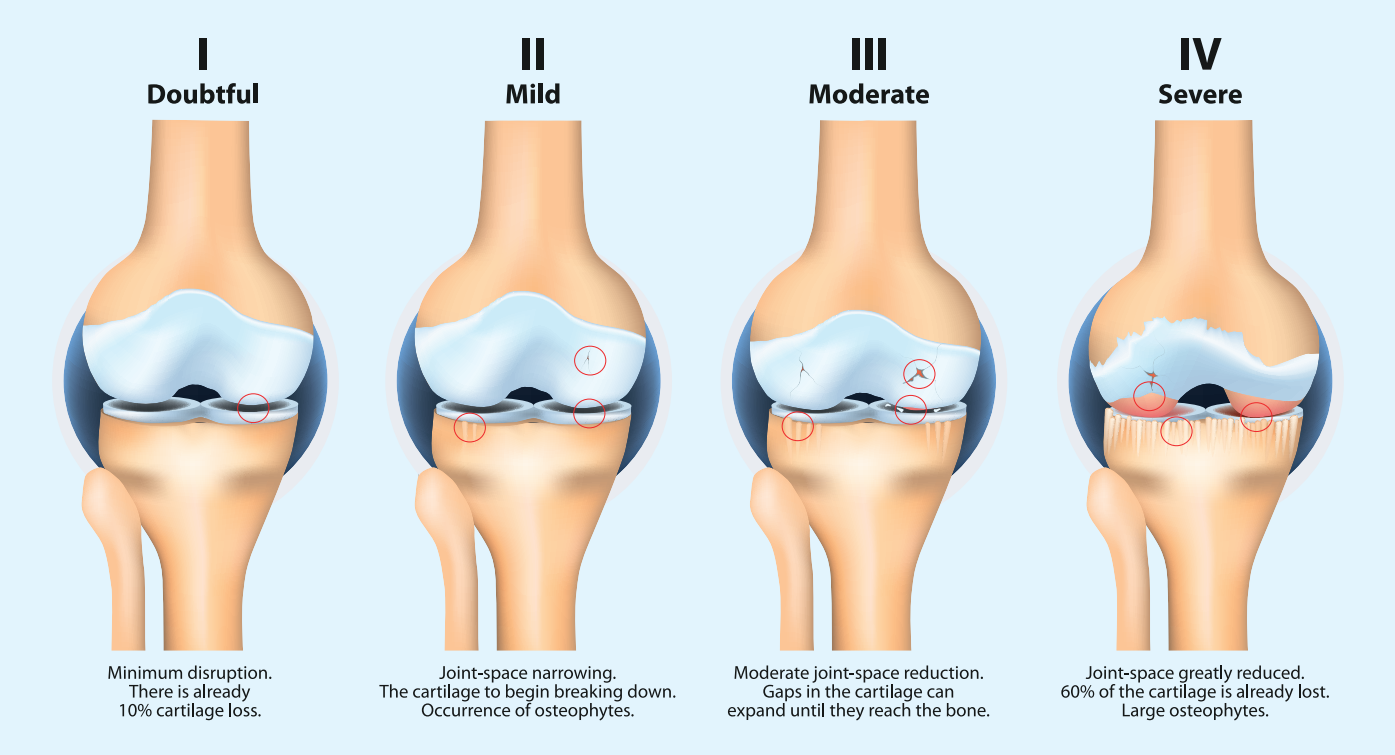
The onset of OA is not limited to ageing, although this population represent the predominant cohort, it can develop from an injury or due to genetic factors. Additional risk factors for OA also include being overweight and engaging in activities that place undue stress upon joints. Before age 45, more men than women have OA, however after age 45, it is more common in women [2, 3]. OA is currently one of the ten most disabling diseases in developed countries. Worldwide estimates are that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA. 80% of those with OA will have limitations in movement, and 25% cannot perform their major daily activities of life [4]. Another aspect of OA care that requires further research is diagnostic techniques. The current methods of clinical diagnosis and X-rays are not precise enough to effectively measure status and progression of the condition, which presents serious difficulties in evaluating both the impact of risk factors and the effectiveness of potential therapies. The lack of valid biomarkers limits pharmaceutical development and clinical monitoring [2].

Research in animal models and clinical analysis of cartilage specimens from patients with OA reveal a sequence of pathological changes in the cartilage matrix associated with OA initiation and progression. In early stage of OA, pathological changes include swelling and degradation of carti-lage matrix in the superficial zone of the cartilage, and increased metabolic activity of chondrocytes [5]. With the progression of OA, the cartilage matrix loses proteoglycans and the collagen network erodes, the synthesis of degradative enzymes (such as matrix metallo-proteinase 13, metalloproteinase with thrombospondin motifs-5) further exacerbates the breakdown of articular cartilage. In addition to cartilage degeneration, the synovial membrane suffers inflammation due to the mechanical changes in OA cartilage, and makes OA more debilitating. In late stage OA, the penetration of vascular elements and sympathetic nerves into the osteochondral layer is evident. Osseous outgrowths called osteophytes often form at the joint margins as well as subchondral bone sclerosis [5].

Living Life with Osteoarthritis

Currently, no effective disease-modifying treatment options are available to cure OA; the existing symptomatic treatments can only relieve pain and improve joint function. According to reports from a prospective, longitudinal cohort study conducted at 53 centres, 54% of OA patients receiving treatment reported inadequate pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs), both traditional NSAIDs (tNSAIDs) and cyclooxygenase 2 (COX-2) inhibitors (COXIBs), are the most frequently prescribed medicines and considered as cornerstones in the treatment of OA [2]. NSAIDS cause a wide variety of adverse effects, such as gastrointestinal reactions, obesity, and osteonecrosis, resulting in limited clinical applications. In severe cases, joint replacement surgery has been proven effective in relieving the painful and debilitating effects of the disease, though the high cost and use of advanced resources mean these procedures are not available in many countries around the world [3, 5].

With OA there is a progressive breakdown of cartilage, with associated pain and consequently a reduction in mobility and range of motion. As the condition proceeds, there can be a breakdown of bone material into splinters, known as spurs.

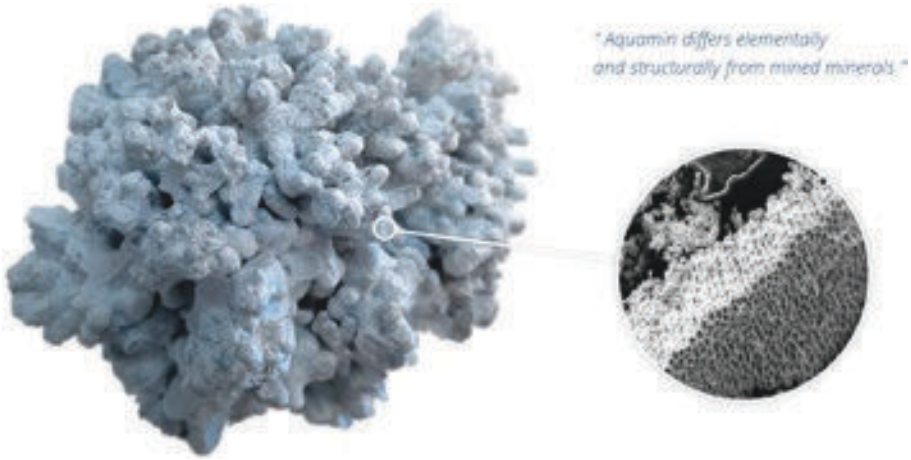


Upregulation of inflammatory cytokines (proteins) and enzymes further degrade cartilage leading to more persistent symptoms. The final stage of the condition sees the cartilage deteriorate to the extent that there is bone to bone contact at the joints.

Aquamin

Aquamin is derived from the cytoskeleton of the red seaweed Lithothamnion sp. Over the course of the seaweed's life, minerals are accumulated from the surrounding seawater, and are stored as carbonate salts in the plant's cell wall. Calcium and magnesium represent one third and over 2%, respectively of the 74 components in the total dry mass of Aquamin. It displays an intricate and unique 3-dimensional structure moulded by the cell wall of the plant. This unique feature is associated with the novel bioactivities attributed to Aquamin when compared with other sources of multi-mineral complexes.

The development of consumer demand for Aquamin was pioneered by Marigot Ltd, by creating awareness and providing innovative research data supporting the inclusion of the 74 marine minerals beneficial for human nutrition. During this time, extensive human studies ensued in an effort to fully evaluate the clinical attributes present within the material, including bioavailability and bioactivity. Aquamin contains a unique trace mineral profile gained from its formation in a marine environment. The elements contained are at trace quantities and are insignificant alone, but within a multi-mineral matrix they work synergistically providing unique and robust bioactivities.



The material has been demonstrated to provide real benefits to sufferers of mild to moderate OA allowing them to perform the daily activities of living, with less pain, increased mobility and less joint stiffness. Scientific studies have shown that Aquamin achieves these improvements in part through the inhibition of NFκB and COX2 activity in a dose dependent manner.

Osteoarthritis Studies

Initial anecdotal reports of the anti-inflammatory effects of Aquamin were conclusively corroborated in two double-blind, placebo-controlled pilot trials in human patients suffering from knee osteoarthritis performed at the Minnesota Applied Research Centre. In the first of these trials [6], 70 subjects with moderate to severe knee osteoarthritis were randomly assigned to one of four 12-week treatment groups. These were 1) glucosamine sulphate (GS), 2) glucosamine sulphate plus Aquamin (G + A), 3) Aquamin (A), 4) placebo (PBO). Patients were assessed using the WOMAC pain score method, and the 6-minute walk test. Patients that consumed Aquamin for the duration of the trial reported less pain in all WOMAC categories, whereas those who consumed glucosamine reported improvement in some symptoms – but not in stiffness. Overall, Aquamin out-performed glucosamine sulphate, and the combination of glucosamine and Aquamin resulted in no significant improvement in pain on the WOMAC score, and was no better than placebo in these parameters. See Figure. Furthermore, 6-minute walk test scores for those patients consuming Aquamin were significantly improved (7%, 101 feet) by the end of the trial, whereas those patients consuming glucosamine sulphate were only able to walk 56 feet further by the end of the trial (see figure).

Osteoarthritis Studies

In a second trial [7], 22 patients with moderate to severe knee osteoarthritis were randomly assigned to one of 2, 12-week treatment groups, 1) Aquamin, and 2) Placebo. Patients were assessed while undergoing gradual reductions in non-steroidal anti-inflammatory drug (NSAID) use. At a 50% reduction of NSAID use, patients in the Aquamin group had improved WOMAC pain scores, passive range of joint motion and 6 minute walk test distances compared to the placebo group. While Aquamin is not a pharmaceutical agent, these data indicate that Aquamin may allow partial reductions in NSAID usage in patients with moderate to severe OA.

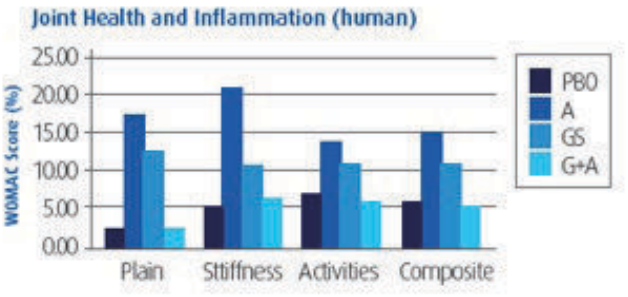


Figure: Aquamin resulted in improved WOMAC scores (i.e. less pain) in all categories.

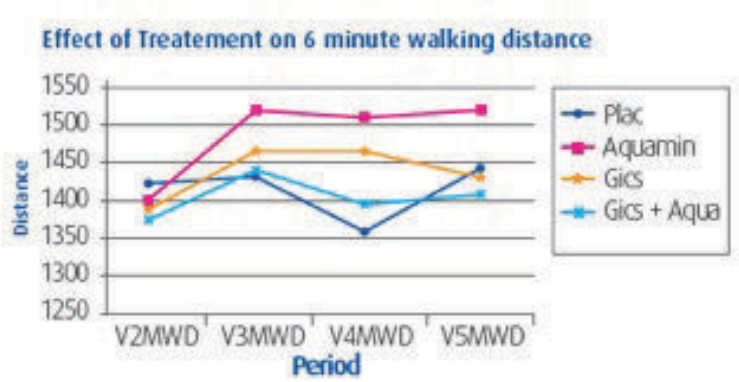


Figure: This demonstrates the improvement in walking distance over a 12 week period on each of the treatments. The most beneficial effects are seen with Aquamin F (pink)

A third trial performed in Ireland [8] indicated that the addition of pine bark and green tea extract to Aquamin further enhanced the anti-inflammatory effects of Aquamin in knee osteoarthritis, as evidenced by significantly lower serum levels of the inflammatory cytokine TNF-α. A series of in vitro studies have shed more light on how Aquamin exerts its anti-inflammatory effects in common and debilitating conditions such as OA. Production of key pro-inflammatory cytokines including TNF- α and IL-1β are inhibited in the presence of Aquamin and an inflammatory stimulus (LPS) [9]. Importantly – the upstream mediator of inflammation, NFκB is also inhibited by Aquamin in a dose-dependent manner, as is the downstream inflammatory mediator most commonly targeted by NSAIDS, COX-2 [10].

Current research on the role of Aquamin in OA is focussing on the assessment of Aquamin on the impact of specific biomechanic paramaters with a role in the improvement of quality of life for OA sufferers. This double blinded placebo controlled intervention study will provide sigificant information on the impact of Aquamin on parameters used clinically to assess manangement of OA symptoms and disease progression.

Marigot Ltd.

Marigot Ltd. was established in 1993 by Les Auchincloss, previously founder and major shareholder of Biocon Limited until acquisition by the Quest Division of Unilever in 1989. Operating under a system that fosters an entrepreneurial approach, the core business involves the identification and development of naturally derived ingredients for the enhancement of human, animal and plant Health.

During the last 24 years, Marigot Ltd has operated with a unique appreciation and mindful understanding of its raw material. The company has worked tirelessly with relevant stakeholders and external parties, ensuring that material is harvested sustainably and with maximum sensitivity to the environment. From this backdrop, Marigot has created and developed the market for this unique marine multi-mineral, covering both the animal health and human food and nutrition sectors. Today, its products are sold in over 40 countries through exclusively appointed distribution partners. A unique facet of Marigot's commitment to its raw material has been its dedication to top-tier peer

reviewed research. The company invests as much as 5-10% of sales turnover annually in research based programs, to further understand the efficacy of this unique, natural mineral source. This approach coupled with processing technology, optimised inclu- sion systems and application development has allowed Aquamin to be successfully included in a wide range of human foods and dietary supplement formulations. The compa- ny can count some of the world's leading blue-chip feed and food producers as its valued customers.

Marigot is clear about the need for science – the requirement to continuously add value and innovate with this unique ingredient through exten- sive research thereby enhancing not only the company's knowledge but ultimately that of its customers. Aquamin represents a novel source of natural multi-minerals which has demonstrated efficacy in influencing health.

In May 2016, Marigot Ltd was awarded Ingredient of the Year (Healthy Ageing) at the Nutraingredients awards at Vitafoods, Geneva. This was in recognition of the strong body of scientific trial data that supports Aquamin and the positive contribution it has made to health.

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