



Aquamin

& Bone Health

Introduction

Bones play many roles in the body including; providing structure, protecting organs, anchoring muscles and storing minerals. While it's important to build strong and healthy bones during childhood and adolescence, it is also essential to maintain bone health during adulthood for wellbeing during ageing and to maintain an active lifestyle. Bones are continuously changing with new bone being formed and old bone being reabsorbed. Up to the age of 30 the body makes new bone faster than it breaks down old bone, therefore bone mass increases. After that, bone remodeling continues, but slightly more material is lost than is formed so bone density decreases therefore, bones become weaker and more susceptible to fracture. Aquamin is a marine derived multi-mineral complex which has been demonstrated to possess unique activity in helping to maintain healthy bone formation. This paper is part of a series outlining the science to date and examining the unique effects of Aquamin and the consequent role that this suite of ingredients can play in addressing common debilitating conditions, such as Osteoporosis, which impede quality of life and put undue strain on overstretched public services.

Osteoporosis

Osteoporosis is the most common bone disease in humans [1]. The condition degrades bone mass and architecture, and impairs the ability of the skeleton to perform fundamental mechanical functions. Osteoporosis leads to weakening of bone strength and an increase in the risk of fractures. Physiologically, osteoporosis occurs due to an imbalance in bone cell activity by which excessive resorption occurs without adequate new bone formation, thereby reducing total bone mass. As a consequence, bone strength is reduced and leads to increased risk of fractures of the vertebrae, hip or wrist. The disease is more common in Caucasians, women, and older people [2]. Osteoporosis causes more than 8.9 million fractures annually worldwide, or one every 3 s, approximately half of which occur in Europe, corresponding with one fracture every 8 s. These 4 million osteoporotic fractures are estimated to cost the EU in the region of €31.7 billion, a figure which is expected to increase to €76.7 billion in 2050 based on the anticipated changes in the demography of Europe [3].



A more practical definition of osteoporosis is based on bone mineral density (BMD). Comparison of the BMD with the average BMD of a person of the same gender at age 30 years is used for diagnostics, and the results expressed in standard deviation units, the so-called 'T-score'. If the T-score is equal to or less than -2.5, osteoporosis may be diagnosed [4]. The lifetime risk for a wrist, hip or vertebral fracture has been estimated to be in the order of 30% to 40% in developed countries which is similar to that for coronary heart disease. Osteoporosis is not only a major cause of fractures, it also ranks high among diseases that cause people to become bedridden with serious complications. These complications may be life threatening in elderly people [5]. Risk factors for Osteoporosis include previous fracture, family history of fracture, slender habitus, early menopause, treatment with drugs known to affect bone (glucocorticoids) and diseases known to affect bone (rheumatoid arthritis). It is now possible to determine an individual's risk of osteoporosis and fracture accurately, and to monitor their response to treatment by bone densitometry. The prediction algorithm FRAX™ allows estimation of 10-year risk and treatment guidance can be based on this. Many cases of osteoporosis are preventable, and treatment is effective in reducing the number of further fractures in patients with established osteoporosis.

Patients at the highest risk for fracture benefit from many licensed treatments. Drugs either inhibit bone resorption or stimulate bone formation. Most drugs approved for use in osteoporosis inhibit bone resorption (e.g. hormone replacement therapy (HRT), bisphosphonates) and usually result in an increase in bone mineral density and a reduction in fracture risk. Osteoporosis can be prevented in people who have osteoporosis but not yet a fracture (primary prevention) and people who have already had a fracture (secondary prevention). These treatments are usually given for secondary prevention and treatment according to the National Institute of Health and Care Excellence guidance. Primary prevention of osteoporosis can be achieved by careful attention to exercise and nutrition [4].

Public Health Recommendations

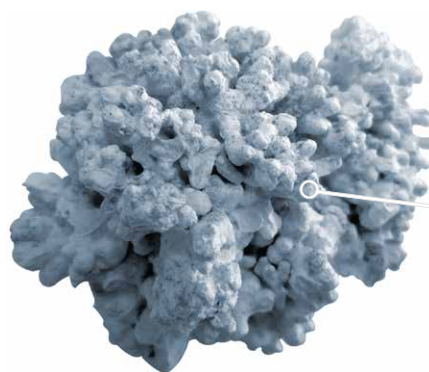
The WHO guidance for osteoporosis is that population-based (i.e. public health) prevention programmes are appropriate for all Member States. Global programmes should include attention to nutritional factors, particularly related to adequate intakes of calcium and vitamin D. Cigarette smoking should be avoided, not solely because of its possible effects on skeletal metabolism, but for the many other adverse effects associated with smoking. Preventing excessive alcohol consumption and the avoidance of immobility are also recommended as public health measures [5].

Due to the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence [5]. The risk of developing osteoporosis depends on how much bone mass is attained by 30 years of age and how rapidly it is lost after that. The higher the peak bone mass, the less likely the development of osteoporosis is during ageing [2]. However, measures to support bone health are essential to reduce the risk of developing the disease. Calcium and vitamin D intake are the cornerstones in the delay/prevention of osteoporosis [6]. The current International Osteoporosis Foundation recommendation for daily calcium and intake for women aged 19-50 years and men up to 70 years is 1000mg/day. For women 51+ years and men >70 years recommended intake is 1200mg/day [7]. The recommended daily allowance of vitamin D is 600IU/day up to 70 years and 800IU/day >70 years [7]. Calcium 1000 mg/day and vitamin D 800 IU/day given together have been shown to prevent hip fracture in housebound, elderly patients. However other studies have suggested that the current available evidence in fracture prevention by calcium supplementation is weak [8]. This treatment is safe and inexpensive, and does not require monitoring. It is commonly given with other treatments for osteoporosis [5].

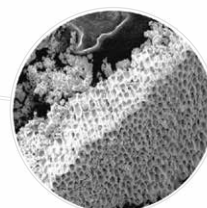
Aquamin - Unique Marine Multimineral Complex

Aquamin is a marine plant multi-mineral complex, derived from the cytoskeleton of the red seaweed *Lithothamnion* sp. It is sustainably harvested from the pristine waters off the northern coast of Iceland and is used extensively in fortification of food and nutraceutical applications. Aquamin is supplied in several grades and is suitable for a wide range of formulations. Over the course of the seaweed's life, minerals are accumulated from the seawater, and stored as carbonate salts in the plants cell wall. Calcium and magnesium represent one third and over 2%, respectively of the 74 components in the total dry mass of Aquamin. Aquamin has an intricate and unique 3-dimensional structure molded by the cell wall of *Lithothamnion* sp. 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 animal and human nutrition in



"Aquamin differs elementally and structurally from mined minerals."



their diet. 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.

Aquamin is harvested under an exclusive license in the cool, clean and pristine waters off the coast of Iceland. In an area untouched by international shipping and industry. In this region the warm waters of the gulf stream meet the cold clean waters of the arctic thus providing the perfect conditions for deposits of Lithothamnion to grow. Marigot meet and exceed the highest international standards to ensure that the material is harvested in a sustainable manner and that this precious resource is protected for future generations. An extensive quality control programme ensures traceability, quality and consistency for each batch.

Aquamin and Osteoporosis

The role of Aquamin in bone health is grounded in excellent science demonstrating real effects in increasing bone strength. Aquamin assists in maintaining bone health in a number of ways including;

- ✓ Providing a bioavailable source of calcium and other essential trace minerals
- ✓ Enhancement movement / physical activity by reducing symptoms associated with inflammation.
- ✓ Influencing biochemical bone turnover markers.

Aquamin is a rich source of minerals essential to life and to numerous critical biochemical pathways. Calcium has been associated with a central role in the prevention of osteoporosis and Aquamin provides a unique source with proven benefits for bone health. A recent study by Brennan et al., 2017 [3] in an animal model of osteoporosis demonstrated that supplementation with Aquamin resulted in less deterioration of trabecular bone than calcium carbonate. Trabecular architecture is significantly preserved when using Aquamin as compared to calcium carbonate. This is supported by a preservation of the mineral phase of bone, which is mirrored by the improved material properties of the bone [3].

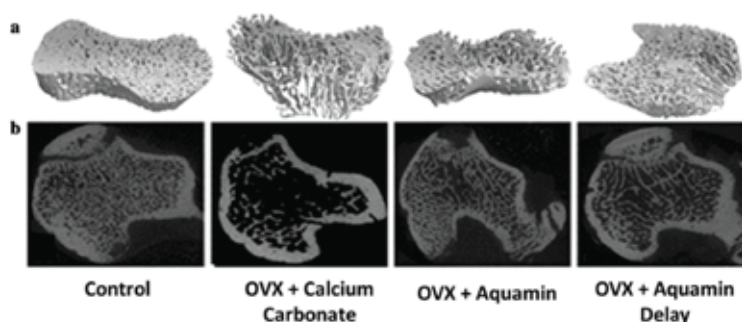


Figure: a) Representative three-dimensional microCT reconstructions and b) two-dimensional slices of trabecular bone from the proximal tibia of rats at week 20. Adopted from [3]

Marigot in conjunction with the University of Ulster undertook a large-scale investigation into mineral supplementation and bone health in post-menopausal women [9]. 300 participants in this trial were evaluated over the course of 24 months for changes in bone density and bone turn-over markers. Treatment groups included a placebo group, a group that was treated with Aquamin only and a group that was treated with Aquamin in combination with a short-chain pre-biotic (fructo oligo-saccharide, scFOS). In summary, a reduction in bone mineral density losses over the course of 24 months was reported in women with osteopenia at the outset of the trial who consumed Aquamin in combination with scFOS. Furthermore, a reduction in bone turnover markers was reported in both those women consuming Aquamin only and in those consuming Aquamin plus scFOS. These findings are indicative of a favourable bone health profile in the population most at risk of osteoporosis and its resulting complications.

Aquamin consumption before and during exercise can offset calcium metabolism disruption associated with exercise in post-menopausal women [10]. Using dampening of serum PTH increases associated with exercise (which will in turn result in bone turnover) as a proxy for calcium absorption, it was demonstrated that Aquamin consumption before and during exercise can reduce exercise-associated calcium metabolic disruption.

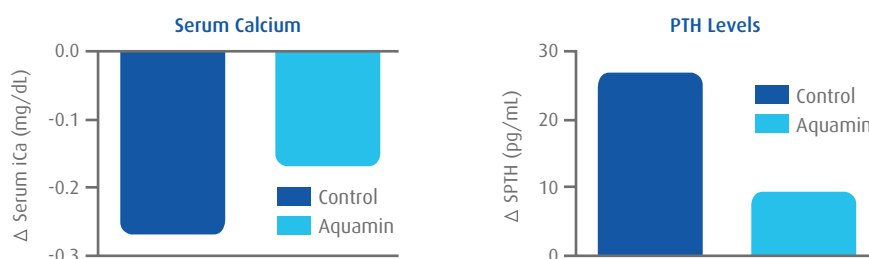
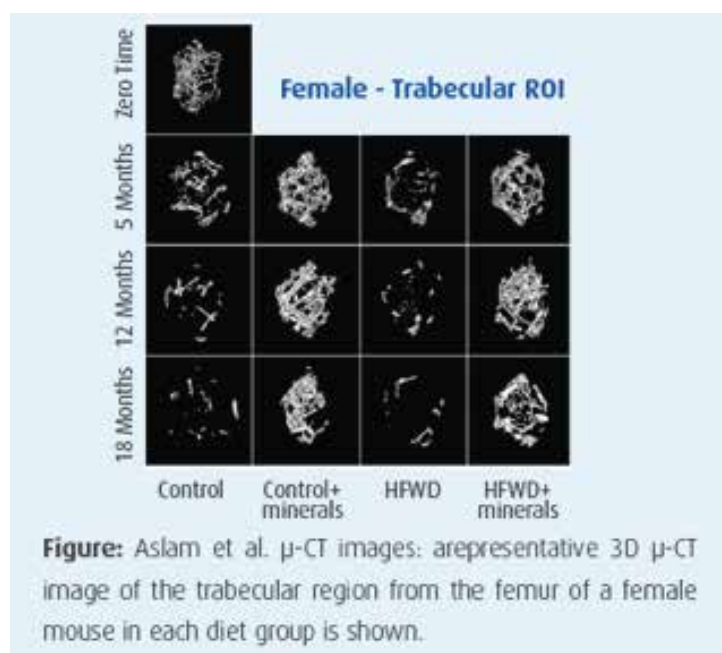


Figure: Shea et al. Changes in Serum Calcium and serum PTH are diminished when Aquamin is consumed (compared to control) in post-menopausal women undergoing a 60-minute brisk walking exercise test.

Researchers at the University of Michigan have investigated the effects of Aquamin in an in vivo model of bone loss – C67BL/6 mice fed a high-fat western diet (HFWD) over time. Aquamin supplementation prevented bone loss and maintained bone strength in mice fed a HFWD, and even resulted in improved bone structure and function compared to mice in the control group (fed a low-fat “healthy” diet) [11]. Further investigations using this model revealed a 5 – 10 fold increase in strontium levels in the bones of Aquamin-treated mice, highlighting the synergistic benefit achieved in supplementation with a natural multi-mineral complex as opposed to single source mined material [12]. Further evidence that minerals besides calcium are important in Aquamin’s beneficial effects on bone health was described by Bae et al., in 2011 [13] through their use of an ovariectomized (to emulate menopause) rat model. In this work, calcium and magnesium from Aquamin out-performed alternative calcium and magnesium sources with respect to bone density preservation. Using a similar model, it has also been demonstrated that co-administration of a probiotic enhanced the performance of Aquamin with respect to bone mineral density [14].



Investigators at the Royal College of Surgeons, Ireland have demonstrated the ability of Aquamin to improve osteoblast (bone cell) mineralisation both in the absence and in the presence of vitamin D. Using an in vitro osteoblast cell culture technique, those cells cultured in the presence of Aquamin demonstrated a three-fold increase in mineralisation compared to those that were cultured without [15]. Using the same model, it has been demonstrated that addition of vitamin D to the culture medium increased both ALP levels and mineralisation over that observed with Aquamin alone, and vitamin D alone [16]. This work highlights the important relationship between Aquamin and vitamin D, and reinforces the recommendation that Aquamin is consumed along with a diet that is replete in vitamin D. Further support for the role of Aquamin in improving bone growth and osteogenesis was published by the RCSI group in 2015 [17].

Current Research

The current research programme for Aquamin in bone health is focused on demonstrating benefits for the prevention of osteoporosis in at risk groups. The research projects are structured to provide further in vitro information on the potential modes of action of Aquamin through the application of advanced proteomics and metabolomics technologies and are supported by in vivo animal and human trials measuring real effects to provide validated support for healthy ageing when using Aquamin in the diet. Preliminary results are promising and provide further validation of the benefits of including Aquamin in diet and nutritional programmes.

Marigot Ltd.

Marigot Ltd. was established in 1993 by Les Auchincloss, previously founder and major shareholder of Biocon Limited until the 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 inclusion systems and application development has allowed Aquamin to be successfully included in a wide range of human foods and dietary supplement formulations. The company can count some of the world's leading blue-chip feed and food producers as its valued customers.

Although numerous anecdotal reports of health benefits associated with consumption of Aquamin existed, no objective research was carried out until Marigot Ltd undertook to understand exactly how Aquamin could impact human health. Marigot Ltd. have accumulated a large and growing body of research evaluating Aquamin in work spanning in vitro assays, numerous animal models and human trials. Today, there are over 25 peer reviewed scientific publications supporting the use of this seaweed in human health including digestive health. Marigot is clear about the need for science – the requirement to continuously add value and innovate with this unique ingredient through extensive 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. Aquamin will continue to be supported by science and grounded in real effects for those who include it in their diet.



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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