AGEING POPULATION STATISTICS

Population ageing is emerging as a key policy issue due to both the proportion and absolute number of older people in populations around the world are increasing dramatically. Japan is currently the only country where the proportion of the population over 60 years exceeds 30%. However, by 2050, many countries will have a similar proportion of older people to that of Japan including countries in Europe and North America, but also Chile, China, the Islamic Republic of Iran, the Republic of Korea, the Russian Federation, Thailand and Vietnam.

The principal drivers of this rapid increase in ageing populations are improved survival at younger ages and increased life expectancy. The pace of population ageing in many countries is also much greater than has been the case in the past [1]. For example, while France had almost 150 years to adapt to a change from 10% to 20% in the proportion of the population that was older than 60 years, places such as Brazil, China and India will have approximately 20 years to make the same adaptation. In Europe the proportion of people aged 65 and older is forecast to almost double between 2010 and 2050 and the number of people aged 85 years and older is projected to rise from 14 million to 19 million by 2020 and to 40 million by 2050. However, the quality of life during these extra years is unclear [4].

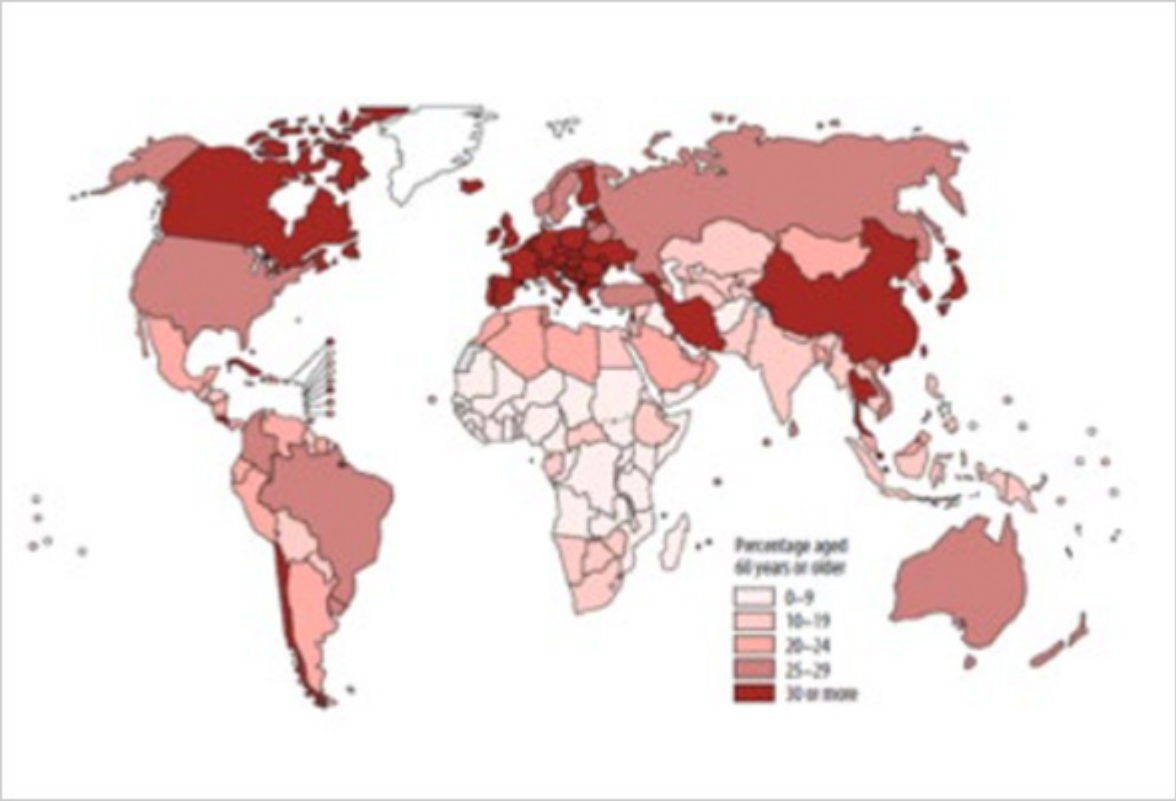

Figure 1: % of world populations 60 years or older by 2050. Adopted from [1]

OSTEOPOROSIS

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 maybe 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 densitome- try. The prediction algorithm FRAXTM 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].

HEALTH CONCERNS RELATED TO AGEING

Movement, sensory function, cognitive function, immune system and skin function are the principal health concerns associated with healthy ageing in the absence of other co-morbidity factors [1]. Muscle mass tends to decline with increasing age, and this can be associated with a decline in

physical movement [5]. Ageing is also associated with significant changes in bones and joints. Bone density decreases with age, particularly among postmenopausal women, leading to Osteoporosis. This can progress to a point where the risk of fracture is significantly increased, which has serious implications for disability, reduced quality of life and mortality. Hip fractures are a particularly devastating type of osteoporotic fracture, and as a result of population ageing they will become more common, reaching an estimated annual global incidence of 4.5 million in 2050.

The median age-standardized rates of fractures related to osteoporosis vary geographically, with the highest observed in North America and Europe, followed by Asia, the Middle East, Oceania, Latin America and Africa [6]. Cartilage undergoes significant changes with age, when it erodes and fluid around the joint decreases, the joint becomes more rigid and fragile leading to symptoms of osteoarthritis in many cases [7]. These and other age-related declines ultimately impact on broader musculoskeletal function and movement. This is reflected in a decrease in the time someone takes to walk a specified distance. Movement has been demonstrated to be one of the most powerful predictors of future outcomes in older age [8].

The variation from person to person in the decline in cognitive functions with age is influenced by many factors, including socioeconomic status, lifestyle, the presence of chronic disease and the use of medication. There is also some evidence that normal age-related cognitive decline can be reduced (by up to one third) by physical activity [9]. An age-related increase in serum levels of inflammatory cytokines has been linked to a broad range of outcomes, including frailty, atherosclerosis and sarcopenia. Research in mice has indicated that the effective clearance of senescent cells by a healthy immune system may delay many disorders related to ageing [10].

The relationship between a nutrient-poor energy dense diet (e.g. The Western diet pattern), sedentary lifestyle and increased chronic disease risk, has been well established [11]. This dietary pattern is characterized by high caloric density, a high intake of meat (especially red and processed meats) and accompanying saturated fat, an unfavourable n-6:n-3 polyunsaturated fatty acid (PUFA) ratio, a high intake of refined carbohydrates, and a low intake of fruits, vegetables, fiber and phytonutrients. This is a common dietary pattern in the United States and many other so-called ‘‘Western’’ nations. However, it is also a dietary pattern that modernising societies are adopting. This diet typically lacks sufficient dietary fiber, calcium, magnesium, potassium, and the antioxidant vitamins A (as carotenoids), C and E. This kind of dietary pattern not only leads to nutritional deficiencies but also promotes a cluster of metabolic problems including obesity, reduced insulin sensitivity, glucose intolerance, dyslipidemia, as well as systematic inflammation, all risk factors for

the most common age associated diseases that include cardiovascular diseases, particular cancers, type 2 diabetes, among others. [11,12]

RECOMMENDATIONS FOR HEALTHY AGEING

There is growing evidence that key health-related behaviours, such as engaging in physical activity and maintaining adequate nutrition, may exert powerful influences in older age. Engaging in physical activity across the life course has many benefits, including increasing longevity. For example, a recent pooled analysis of large longitudinal studies found that people who engaged in 150 minutes per week of physical activity at moderate intensity had a 31% reduction in mortality compared with those who were less active. The benefit was greatest in those older than 60 years [13]. Physical activity has multiple other benefits in old age. These include improving physical and mental capacities (for example, by maintaining muscle strength and cognitive function, reducing anxiety and depression, and improving self-esteem); preventing disease and reducing risk (for example, of coronary heart disease, diabetes and stroke); and improving social outcomes (for example, by increasing community involvement, and maintaining social networks and intergenerational links) [1]. Ageing is accompanied by physiological changes that can negatively impact nutritional status. Sensory impairments, such as a decreased sense of taste or smell, or both, may result in reduced appetite. Poor oral health and dental problems can lead to difficulty chewing, inflammation of the gums and a monotonous diet that is poor in quality, all of which increase the risk of malnutrition [1].

Although energy needs decrease with age, the need for most nutrients remains relatively unchanged. Malnutrition in older age interacts with the underlying age-related changes de- scribed above, often taking the form of reduced muscle and bone mass, and increases the risk of frailty. Malnutrition has also been associated with diminished cognitive function, a diminished ability to care for oneself, and a higher risk of becoming care-dependent [14]. The evidence suggests that worldwide a sizeable proportion of older people may be affected by malnutrition. Various types of interventions are effective in reversing these patterns of malnutrition. Improving the nutrient density of food, particularly that of vitamins and minerals in order to reduce the impact of malnutrition in an ageing population has been shown to be effective in delaying care dependency, improving intrinsic capacity and reverting frail states [15].

AQUAMIN AND HEALTHY AGEING

The role of Aquamin in healthy ageing is grounded in excellent science demonstrating real effects for the ageing. Biological changes associated with ageing are neither linear nor consistent, and they are only loosely associated with age in years [2]. Many of the mechanisms of ageing are random but are strongly influenced by the environment and behaviors of the individual. Aquamin assists an ageing population to achieve two key enablers for healthy ageing;

- essential mineral nutrition
- enhancement of movement/physical activity by reducing symptoms associated with diseases which have an inflammatory component.

Aquamin is a rich source of minerals essential to life and to numerous critical biochemical pathways. Calcium and magnesium are minerals known to be implicated in biological ageing. Their dietary intake and body concentrations modulate inflammation, oxidative stress, apoptosis, and cellular signalling processes as well as glucose metabolism. Their action on these processes tends overall to be protective. Dietary intake of these minerals is linked to better cardiovascular health, lower risk of stroke and myocardial infarction, and decreased risk of type 2 diabetes. Their influence on brain aging has not been sufficiently studied but the available evidence also suggests that their intake exerts a positive influence on brain health. Evidence while sparse is suggestive of a protective effect of magnesium and calcium, on cognitive decline and risk of dementia in old age. [16]. A diet deficient in essential minerals is associated with a range of diseases including obesity, high blood pressure, high cholesterol, heart disease, type II diabetes, colorectal cancer, liver cancer, and osteoporosis, as well as inflammation and disorders of the digestive system.

The role of Aquamin in enhancing movement/physical activity leading to a more active lifestyle for an ageing population has been studied in the context of osteoarthritis and osteoporosis sufferers. Marigot in conjunction with the University of Ulster undertook a large-scale investigation into mineral supplementation and bone health in post-menopausal women [17]. 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 shortchain prebiotic (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. All of these

findings are indicative of a favourable bone health profile in the population most at risk of osteoporosis and resulting complications.

Aquamin consumption before and during exercise can offset calcium metabolism disruption associated with exercise in post-menopausal women [18]. 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.

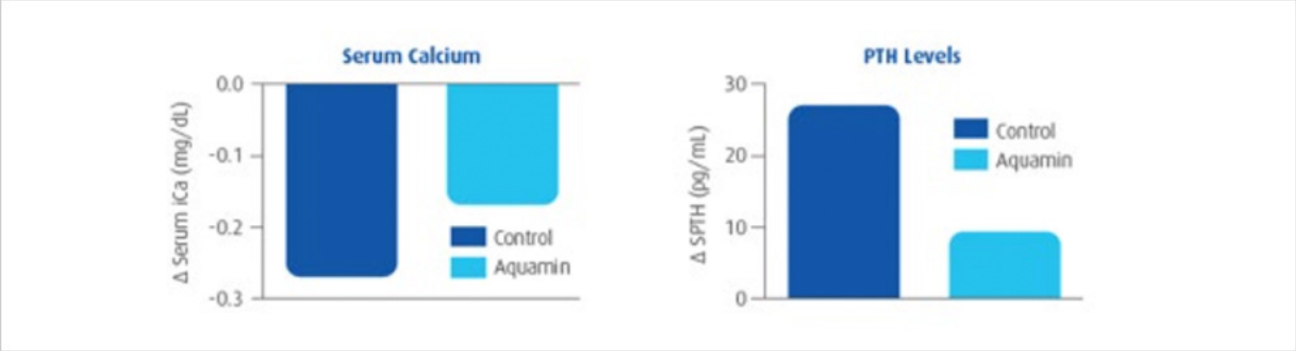

Figure: Shea et al. Changes in Serum Calcium and serum PTH are diminished when Aquamin is consumed (compared to control) in post-menopausal women undergoing a 60-minute brisk walking exercise test.

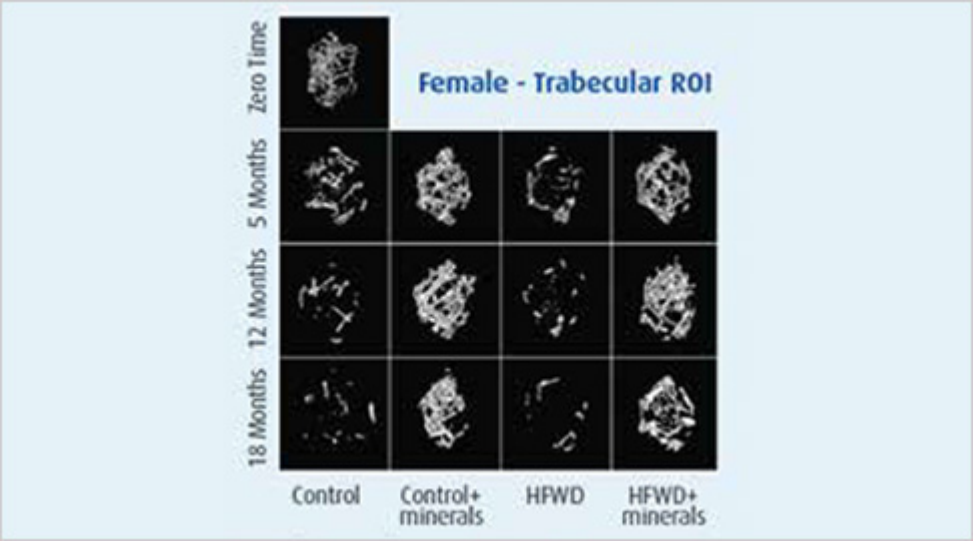

Figure: Aslam et al. μ-CT images: arepresentative 3D μ-CT image of the trabecular region from the femur of a female mouse in each diet group is shown

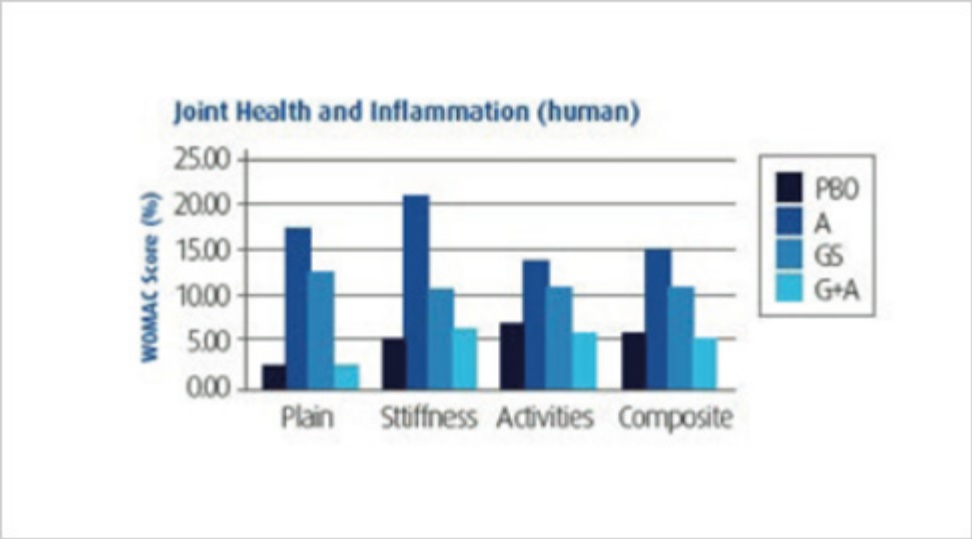

Figure: Aquamin resulted in improved WOMAC scores (i.e. less pain) in all categories.

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) [19]. 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 [20]. Further evidence that minerals besides calcium are important in Aquamin's beneficial effects on bone health was described by Bae et al in 2011 [21] 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-adminstration of a probiotic enhanced the performance of Aquamin with respect to bone mineral density [22].

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 [23]. 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 [24]. 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 [25].

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 [26], 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. 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.

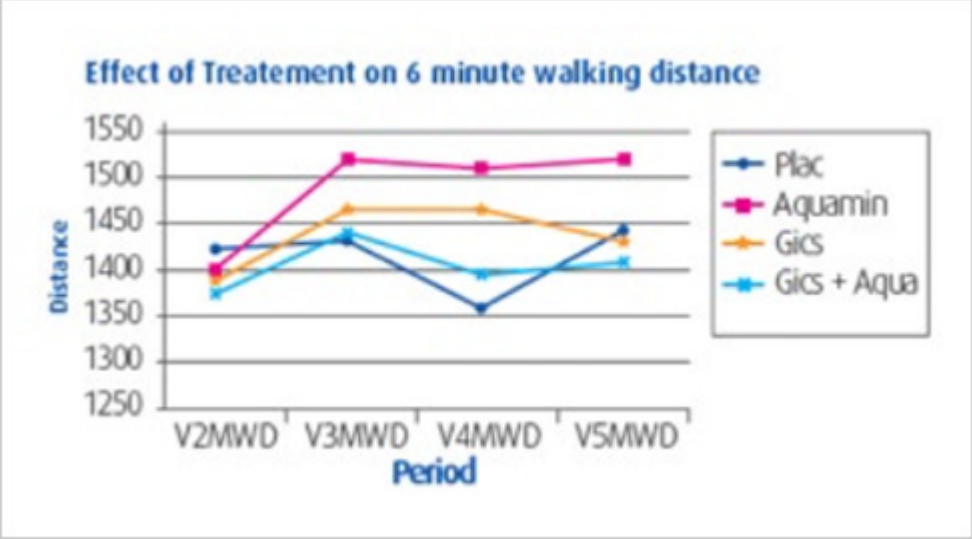

Figure: This demonstrates the improvement in walking distance over a 12 week period on each of the treatments. The most beneficial effects are seen with Aquamin F (pink)

In the second trial [27], 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.

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 osteoarthritis. Production of key pro-inflammatory cytokines including TNF- α and IL-1α are inhibited in the presence of Aquamin and an inflammatory stimulus (LPS) [28]. Importantly, the upstream mediator of inflammation, NFαB is also inhibited by

Aquamin in a dose-dependent manner, as is the downstream inflammatory mediator most commonly targeted by NSAIDS, COX-2 [29].