HA Tech 2.0® Hyaluronan: a step ahead in sport nutrition and healthy ageing for bone and joint health

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The global bone and joint supplements market is projected to overcome US$ 5 Billion by 2025 and is projected to grow at a CAGR of 6.7% with a significant momentum for joint segment, displaying a potential growth at over 7.2% (1). Due to a greater life expectancy worldwide, the incidence of acute or chronic osteo-articular diseases is rising (2). Attributable incident factors are both endogenous (age, sex, weight, genetics) and exogenous (joint injuries, medications), assisted by cofactors such as activity habits, nutritional status (e.g. eating disorders, celiac disease, calcium, vitamin D, protein intake), smoke and alcohol. They all contribute to joint-related pathologic conditions, such as osteoarthritis, a serious rheumatic musculoskeletal disorder affecting about 3.3% to 3.6% of the population globally, and causing moderate to severe disability in 43 million people, and osteoporosis, a health condition that silently weakens the bones, making them fragile and more likely to break (3, 4).

Osteoarthritis (OA), the most common form of arthritis, is a degenerative joint disease, whose complex and multifactorial aetiology bridges biomechanics and biochemistry. OA shows reduced hyaluronic acid (HA) concentration, cartilage disruption, local inflammation of tendons, decreased synovial fluid, osteophyte formation and muscle weakness. It damages the entire joint, triggering tissue changes and biomechanical stress, limiting mobility and interfering with daily activities (5, 6).

Normal articular cartilage has a unique load-support mechanism governed by collagen-proteoglycan matrix, with its high water content, stiffness and permeability. Changes in cartilage composition and molecular organization alter the balance of biomechanical properties,

causing excessive cartilage deformation and structural loss, leading to cartilage erosion, the cardinal OA pathologic feature (6).

OA shares the same important determinants (e.g. estrogen deficiency in women) and solutions (modification of physical activity and dietary calcium/vitamin D intake) with osteoporosis, and evidence suggests an inverse relationship between these pathologies: high bone mineral density is associated with an increased prevalence of hip, hand, and knee OA and may protect against disease progression. Women with high lifetime exposure to estrogen have high bone mass, which appears to increase the risk for knee and hip osteoarthritis (2, 6).

Bone mineral content represents the reference index for osteoporosis diagnosis, together with several biochemical markers of bone turnover. A similar approach is used to develop synovial fluid and other bio-markers to study cartilage turnover and synovial inflammation in OA (2, 6).

OA management is largely palliative. Indeed, there is no cure for it. Focus is on symptoms alleviation and life quality improvement. Current recommendations for OA management, together with prevention, include a combination of pharmacological and non-pharmacological approaches (7). The most common choice is pharmacological: non-steroidal anti-inflammatory drugs (NSAIDs – e.g. Diclofenac) and Acetaminophen (Paracetamol) show comparable effects (8). In case of NSAIDs intolerance or inefficacy, corticosteroids injections and opioids are alternatively used (5).

One-third of patients permanently taking NSAIDs suffer from gastric or duodenal ulcers (9). Cycloossigenase-2 (COX-2)-specific inhibitors, or nonselective NSAIDs with gastroprotective therapy, are then alternatives for OA medical management. In case of pharmacology treatments inefficacy, surgical approach is selected. However, total joint replacement has limited durability due to aseptic loosening and osteolysis risk, asking for new interventions in people with long life expectancy. In the end, both active and passive (physiotherapy) exercise represent an effective plus in OA to limit inactivity and positively affect metabolism and muscular balance (8).

Due to serious adverse effects associated with the long-term use of pharmacological therapies, patients often look for safer and effective therapeutic alternatives (e.g. herbs, nutrition, homeopathy and acupuncture) to reduce pain and gain joint stability and mobility (7). For instance, topical analgesics such as capsaicin cream are used in case of hand or knee OA, with mild to moderate pain.

The development of administrable cartilage repairs, synovial fluid stimulants and anti-inflammatory agents, together with their ease of use and noninvasiveness, represents the goal to be achieved (8).

Together with Devil's claw (*Harpagophytum procumbens*), turmeric (*Curcuma longa*) and bromelain, *Boswellia serrata extract* (BSE) is indicated as a nutraceutical active with promising antiphlogistic and analgesic function. Used to treat OA, BSE showed good results in terms of pain reduction and improved physical functioning (9) and its association with hyaluronan (5) showed positive results, thanks to the association of anti-inflammatory and synovial fluid reconstituting effect of the two actives.

Together with hyaluronan (HA), N-acetyl-D-glucosamine (NAG - HA natural precursor), chondroitin sulphate (CS) and collagen peptides are nutraceuticals that became popular for their chondroprotective and osteotropic activities. Investigations on both systemic and local administration have demonstrated their supportive role and efficacy in counteracting signs and symptoms of OA. Furthermore, HA and NAG can significantly reduce OA progression (5).

Within conventional approaches, collagen peptides supplementation stimulates joint health, reducing stiffness and discomfort associated with OA. They regulate bone turnover

processes too, acting on osteoblast and osteoclast activity in extracellular bone matrix, the essential framework for calcium mineralization.

Naturally present in the body, NAG and CS are involved in normal cartilage repairing and maintenance, exerting therapeutic effects in treating OA by providing substrate for reparative processes. Absorbed from the gastrointestinal tract, appear to be capable of increasing proteoglycan synthesis in articular cartilage. Literature reports their favorable effects (8), upregulating hyaluronan synthesis in human articular chondrocytes and mediating anti-inflammatory pathways. Despite NAG and CS showed a reduction in the deterioration of cartilage by stimulating proteoglycans synthesis and proteolytic enzymes inhibition, literature shows no great differences in pain and function comparing treatments with the placebo (10).

To increase OA joints functionality, reduce pain and improve life quality, the aim is to restore tissues integrity and reduce inflammatory status. Due to its chondroprotective and anti-inflammatory effect, HA represents a reliable solution. It is a linear polysaccharide consisting of alternating disaccharide monomers of N-acetyl-D-glucosamine and D-glucuronic acid, joined by glycosidic bonds. It is characterized by a high molecular weight, where the basal unit is repeated from 2000 to 25000 times, resulting in a molecule length from 2 to 25 µm. Ubiquitously spread in human body, HA is an important constituent of the extra- and peri-cellular matrix and it is especially found in the connective, epithelial and nervous tissue. Extensively used in health care, cosmetic and pharmaceutical industries, HA is proposed as a viscosupplement, as a sterile jellified injectable solution, to relieve OA signs and symptoms, thanks to its physiological role in synovial fluid (5). Besides its intra-articular injection, it can be also orally administered, in order to restore synovial viscoelasticity and maintain, protect and stimulate joint cartilages biosynthesis through an effective and tolerable solution, in addition to its anti-inflammatory and analgesic effect.

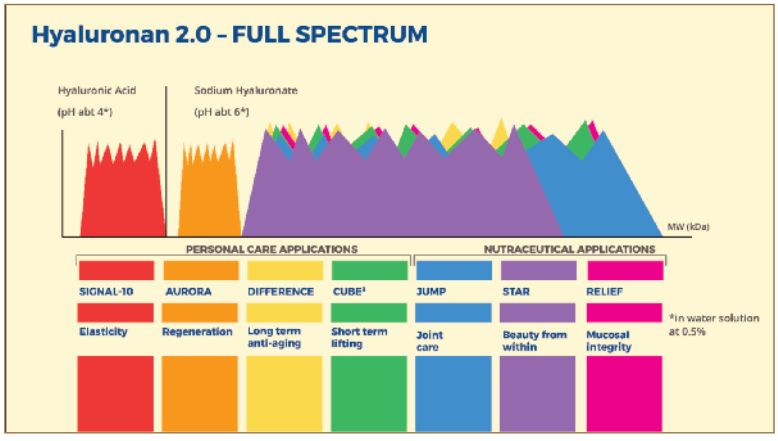

Figure 1 – Full Spectrum Technology.

Few published papers have reported significant improvements in symptoms and articular functionality in patients taking hyaluronans orally and evidence suggested that polymers with different molecular weights have different bioavailability and effective profiles. Indeed, different length chains behave differently: oligosaccharides have angio-genetic effects, low-weight polysaccharides have proliferative effects, while medium-high chains induce quiescent response. Furthermore, intrinsic properties of polysaccharides such as anti-oxidant and anti-inflammatory activity, higher for lower molecular weights, are improved during enzymatic metabolism by the activation into smaller fragments. Some *in-vitro* studies showed that low and high molecular weight HA used together have a biological synergistic effect if compared to the single molecular weight alone. Indeed, literature reports that orally administered HA could have limitations due to its molecular weight (5), influencing molecule's activity and bioavailability, and the administration of a single HA molecular weight based supplement shows then limits in terms of efficacy. Anyhow orally administrable HA solutions against OA

symptoms represent an effective and valid solution to intra-articular injection: besides its invasiveness, current literature reports inconsistent results regarding HA injection efficacy for knee OA treatment, due to intrinsic differences between individual HA products. Indeed, several formulations are approved for clinical use and these differ in HA origin, manufacturing process, chemical-physical properties (molecular weight and final concentration), joint space half-life, rheological properties, administration schedules and cost.

Together with OA and osteoporosis, tendinopathies represent another group of joint related pathologies which are both a consequence in sports and working population and a limit to physical activity, affecting quality of life. Besides its effect against OA, HA has been proved to be effective on bone mass increasing and both tendon gliding and architectural organization improvement (11). Moreover, considering oxidants role in triggering OA and reactive oxygen species (ROS) sourced from chondrocytes activity, the association of HA and

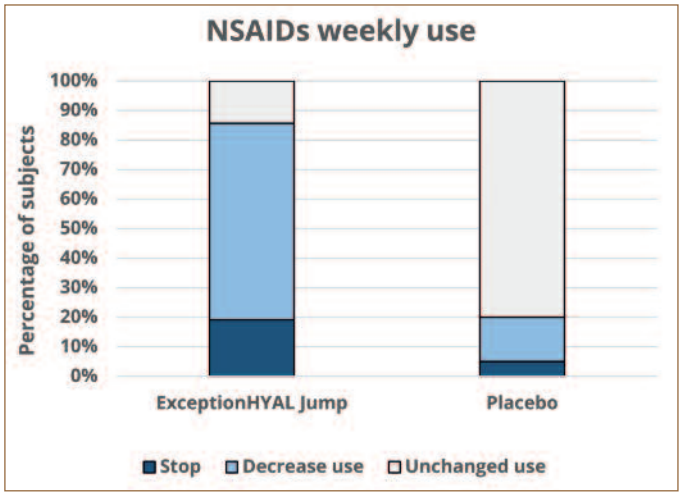

Figure 2 – NSAIDs weekly use.

anti-oxidant micronutrients (e.g. vitamin C, astaxanthin) could further support cartilage collagen and synovial fluid hyaluronate protection. Due to its effect on bone metabolism and on chondrocytes, vitamin D has a recognized role in sport nutrition supplementation too (6).

Because of low bioavailability and chain length-specific effect of hyaluronan, Roelmi HPC has developed the Full Spectrum Technology (FST) based on a fine modulation of the bio-fermentation production process, to obtain a wider spectrum of hyaluronan molecular weights (Figure 1), called HA Tech 2.0®. Based on outcomes from *in-vitro* and *ex-vivo* tests, carried out to demonstrate ingredient bioavailability, stability, anti-inflammatory and antioxidant efficacy, and together with clinical trials carried out to confirm the efficacy profile in humans, HA Tech 2.0® has demonstrated to meet customer needs with targeted products for specific health concerns. Within the products line, ExceptionHYAL® Jump has been specifically formulated to counteract OA progression and improve joint health and quality of life, reducing NSAIDs use (Figure 2).

In a double-blind randomized placebo-controlled clinical trial, administered at 200mg/day to patients suffering from knee OA symptoms, it showed to improve pain, joint functionality and stiffness. The superiority of FST is due to a higher affinity with cell-receptors, which allows to promote endogenous synthesis of hyaluronic acid, indeed resulting in a more performing efficacy profile of this hyaluronan complex when compared to standard HA. Such approach through an orally administrable and effective Full Spectrum-HA allows a better compliance for patients, representing a cost-saving and less invasive solution for knee OA treatment if compared to injectable treatments.

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