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Research Progress on the Application of Hyaluronic Acid in Improving Skeletal Joints and Sports Nutrition

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Abstract. Hyaluronic acid (HA; colloquially "玻尿酸" in Chinese) is a linear polysaccharide composed of alternating units of glucuronic acid and N-acetylglucosamine. It is a natural constituent of human connective tissues, skin, synovial fluid, and the vitreous body of the eye. After extraction and purification, HA can be used for moisture retention and water-locking, anti-aging and dermal filling/contouring, joint lubrication and cushioning, and to promote wound repair. This paper provides a detailed overview of the mechanisms and efficacy of hyaluronic acid in the treatment of osteoarthritis and other musculoskeletal disorders.

Keywords: Hyaluronic acid, skeletal joints, sports nutrition, research progress

1. Introduction

Hyaluronic acid (HA) is a linear polysaccharide composed of alternating units of glucuronic acid and N-acetylglucosamine. It is widely distributed in the skin, synovial fluid, vitreous body, and the extracellular matrix (ECM) of skeletal muscle. With its remarkable water-retention capacity and viscoelasticity, HA plays a central role in tissue lubrication, as well as in the regulation of cell migration, proliferation, and differentiation. At present, clinical and basic research on HA has primarily focused on three major areas: skin hydration and anti-aging, supplementation of joint viscoelasticity, and wound repair. While there is relatively comprehensive evidence-based support for its efficacy in classical applications such as moisturizing and joint lubrication, studies on its role in skeletal and skeletal muscle homeostasis, injury repair, and functional enhancement remain scattered and lack consensus. Therefore, writing a review focused on the research progress of HA in improving skeletal joints and sports nutrition is of pressing significance, as it helps to fill current knowledge gaps and provides guidance for future basic and translational research.

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2. Overview of hyaluronic acid

2.1. Structure and properties of hyaluronic acid

2.1.1. Chemical structure and molecular weight

Hyaluronic acid (HA) is a naturally occurring, non-sulfated, non-protein glycosaminoglycan composed of alternating units of N-acetyl-D-glucosamine and D-glucuronic acid, and it possesses excellent biocompatibility and biodegradability [1]. The disaccharide units are linked by β-1,3-glycosidic bonds, while multiple disaccharide units are further connected by β-1,4-glycosidic bonds, forming a linear molecular chain with the repeating unit ((1→3)-β-D-GlcNAc-(1→4)-β-D-GlcUA-).

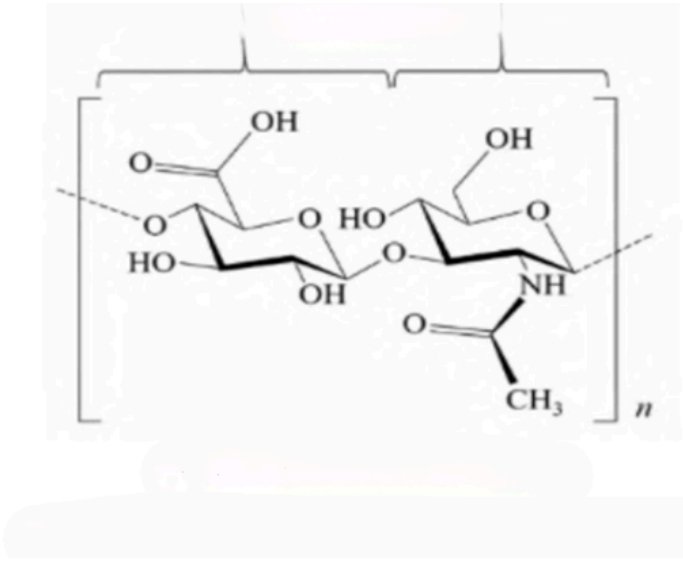

Figure 1. Chemical structure of hyaluronic acid

The spatial conformation of HA exhibits a two-fold helical structure, stabilized by numerous intramolecular hydrogen bonds, which confers rigidity and structural stability. In aqueous solutions, HA molecules adopt an expanded random-coil conformation. At low concentrations, the molecular chains become entangled, giving rise to a three-dimensional network structure. The molecular weight of HA shows a wide distribution, ranging from several thousand to several million Daltons.

2.1.2. Physicochemical properties

HA appears as a white amorphous solid, odorless and tasteless, readily soluble in water but insoluble in organic solvents. It is characterized by high viscosity, strong elasticity, and excellent water-retention ability. Aqueous solutions of HA typically exhibit non-Newtonian fluid properties.

2.1.3. Biological functions

HA performs multiple essential biological functions in vivo, including maintaining the structure and function of the extracellular matrix, regulating cell metabolism and proliferation, and participating in wound healing and inflammatory responses. With its outstanding water-retention, lubricating properties, and biocompatibility, HA is widely applied as an exogenous medical adjunct in the treatment of arthritis, promotion of soft tissue regeneration, and medical aesthetics.

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2.2. Sources and preparation of hyaluronic acid

2.2.1. Natural sources

The natural sources of hyaluronic acid (HA) are primarily derived from bone broth, particularly from chicken or bovine bones, in which prolonged simmering releases HA into the broth. In addition, chicken combs and other animal cartilage are rich in HA. Cartilage contains not only HA but also abundant collagen, both of which contribute to joint health. Certain cruciferous vegetables, such as cabbage and kale, are rich in vitamin C and magnesium, which promote the biosynthesis and maintenance of HA in the body. Among fruits, citrus varieties such as lemons, oranges, and grapefruits are high in vitamin C, which not only participates directly in HA synthesis but also inhibits its degradation. Legumes, including soybeans and black beans, are rich in isoflavones that help increase endogenous HA levels. Foods high in zinc, such as shellfish, pumpkin seeds, and sesame, are also beneficial for HA synthesis, since zinc is an essential mineral cofactor in the biosynthetic process of HA.

2.2.2. Synthetic methods

The main artificial methods for HA production include microbial fermentation, enzymatic synthesis, and solid-phase synthesis. Microbial fermentation is the most widely applied method in current HA production. This approach requires selecting suitable microbial strains, commonly including Streptococcus, Pneumococcus, and Lactobacillus. The fermentation medium is supplemented with carbon sources, nitrogen sources, and auxiliary nutrients to support microbial growth and HA synthesis. The fermentation period usually lasts 3–7 days, after which the bacterial biomass containing HA is harvested by centrifugation. To extract HA, the bacterial cells are either lysed directly or subjected to partial enzymatic hydrolysis. Common extraction techniques include hydrolytic extraction, where bacterial cells are hydrolyzed to release HA followed by separation through centrifugation or filtration, and alkaline extraction, where cells are dissolved in an alkaline solution and HA is obtained through precipitation, washing, and centrifugation.

Enzymatic synthesis employs simple sugars such as glucose as raw materials. Under cascade catalysis by multiple enzymes, precursor molecules such as sugar nucleotides are generated. These precursors are then polymerized into HA under the action of hyaluronan synthase.

Solid-phase synthesis involves attaching an initiating monomer to a solid support, followed by the sequential addition of protected monosaccharide units and coupling reagents. Each reaction step is followed by washing to remove unreacted reagents and byproducts. Once chain assembly is completed, HA is cleaved from the solid support and subsequently purified.

2.2.3. Safety, regulatory frameworks, and application fields

HA is an endogenous component of the human body and demonstrates excellent biocompatibility and safety. When used appropriately, it generally does not produce significant toxic or adverse effects. From a regulatory perspective, HA production and application are strictly supervised in China by relevant authorities. Internationally, regulations differ across countries and regions, but the consensus is that HA is safe and valuable for medical and consumer use. Medical field: HA is widely used in ophthalmic surgery, treatment of joint diseases, and wound repair. Cosmetic field: HA functions as a moisturizer and skin-conditioning agent in a variety of skincare formulations.

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Food field: HA can be applied as a thickening agent and as a nutritional supplement in health-related food products.

3. Applications of hyaluronic acid in skeletal joint improvement

3.1. Hyaluronic acid and sports-related joint injuries

The mechanisms of sports-related joint injury can generally be categorized into three types: mechanical trauma, inflammatory cascade, and failure of synovial lubrication. Mechanical trauma occurs when acute impact or repetitive shear stress leads to rupture of collagen fibers in the cartilage matrix and loss of proteoglycans. Inflammatory cascade is triggered by minor initial damage that releases danger-associated molecular patterns (DAMPs), which signal the immune system to release inflammatory mediators such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). As these factors accumulate, they indiscriminately attack joint tissue, with matrix metalloproteinases (MMPs) degrading both collagen and hyaluronic acid (HA) in the cartilage. The degradation products themselves act as new DAMPs, perpetuating a vicious cycle of chronic inflammation. Failure of synovial lubrication occurs when the molecular weight and concentration of HA decline, leading to the loss of boundary lubrication. The consequent increase in the friction coefficient results in secondary cartilage damage.

3.2. Hyaluronic acid and Osteoarthritis (OA)

3.2.1. Pathological mechanisms of osteoarthritis

Osteoarthritis (OA) is a multifactorial degenerative joint disease, with etiology related to genetic predisposition, aging, trauma, obesity, sex, and other risk factors [1]. Its pathological mechanisms involve cartilage degeneration, synovitis, and subchondral bone remodeling, among other pathological changes.

3.2.2. Protective effects of HA on articular cartilage

HA exerts protective effects on articular cartilage through several mechanisms. It enhances chondrocyte viability and proliferation, thereby promoting regeneration of damaged cartilage tissue. HA also regulates inflammatory responses by suppressing the release of pro-inflammatory cytokines, reducing cartilage inflammation, and facilitating repair. In addition, HA promotes collagen synthesis, increases the water content of the extracellular matrix (ECM), and improves the mechanical properties and shock resistance of cartilage tissue [2].

3.2.3. Effects of HA on synovial fluid

HA significantly improves the viscoelasticity of synovial fluid. A single intra-articular injection of 8–10 mg high-molecular-weight HA (HMW-HA) can restore the elastic modulus of synovial fluid to approximately 80% of the pre-injury level. Furthermore, HMW-HA promotes chondrocyte migration and localization to the site of injury through activation of Rho GTPases and cytoskeletal reorganization signaling pathways, thereby enhancing matrix synthesis and tissue reconstruction at the lesion site [3]. Intra-articular injection of low-molecular-weight HA (LMW-HA) has been shown to reduce reactive oxygen species (ROS) levels in the synovial fluid of OA patients [4]. Additionally,

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HA-protein complexes (lubricin/HA) form a “brush-like” hydrated layer at the cartilage–cartilage interface, reducing the coefficient of friction by 30–50%.

3.2.4. Analgesic effects of HA

HA also demonstrates analgesic properties. By covering exposed nociceptive nerve endings, HA reduces mechanical sensitivity, while also inhibiting the release of substance P. In terms of central modulation, HMW-HA can downregulate the expression of transient receptor potential vanilloid 1 (TRPV1) in the dorsal horn of the spinal cord via CD44, thereby reducing pain sensitization. Clinical evidence from a meta-analysis (n = 2,867) indicates that HA injections reduce visual analogue scale (VAS) pain scores by an average of 2.1 points (95% CI: 1.8–2.4), with therapeutic effects lasting for ≥6 months.

3.3. Hyaluronic acid and Osteoporosis (OP)

3.3.1. Pathological mechanisms of osteoporosis

Osteoporosis is a common metabolic bone disease characterized by microarchitectural deterioration, reduced bone mass, and decreased bone strength [HQM]. It is closely associated with reductions in bone mineral content and structural integrity, making it a major cause of fragility fractures [5]. Osteoporosis is generally classified into two categories: primary osteoporosis and secondary osteoporosis [6,7]. Primary osteoporosis is preventable and treatable, and timely, effective interventions can significantly reduce fracture risk [8,9]. The underlying pathological mechanism involves imbalance of bone remodeling. Overactivation of the RANKL/OPG signaling axis promotes osteoclastogenesis, while dysregulation of the Wnt/β-catenin pathway reduces osteoblast differentiation and activity, tipping the balance toward bone resorption. With global population aging, osteoporosis has emerged as a major public health challenge, with prevalence and progression rates steadily increasing worldwide. Its hallmark clinical manifestation is loss of bone mineral density (BMD) [10].

3.3.2. Regulatory effects of HA on bone metabolism

The imbalance between osteogenesis and bone resorption is considered a key mechanism not only in local bone destruction associated with knee osteoarthritis (KOA) but also in systemic bone loss. This imbalance manifests as aberrant bone remodeling, abnormal osteoclast activation, and disrupted bone turnover, which are further reflected in altered serum markers of bone metabolism [11]. Sodium hyaluronate (SH) therapy has been shown to improve bone metabolic homeostasis, attenuate inflammatory responses, and promote functional recovery of the knee joint, while maintaining a favorable safety profile. Clinical studies report that SH injections reduce serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and type II collagen C-terminal telopeptide (CTX-II), while elevating osteoprotegerin (OPG) levels. These findings support the anti-inflammatory effects of HA in the joint cavity and its positive impact on systemic bone metabolic markers [12]. Moreover, arthroscopic debridement combined with triamcinolone and SH injections has demonstrated superior efficacy in KOA patients. This multimodal approach synergistically suppresses inflammation, inhibits bone resorption, enhances bone formation, and substantially alleviates pain and functional impairment, offering valuable clinical applicability [13].

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3.3.3. Effects of HA on bone mineral density

The primary function of sodium hyaluronate (SH) in joints is to enhance the viscosity and lubrication of synovial fluid, thereby protecting cartilage by preventing direct contact with inflammatory mediators. SH also inhibits the release of inflammation-related enzymes and reactive oxygen species (ROS), reduces synovial permeability and intra-articular effusion, and ultimately slows down cartilage destruction. Bone mineral density (BMD) is largely regulated by mechanical loading derived from muscle-generated stress. Mechanical forces stimulate osteocytes and promote new bone formation, whereas reduction or absence of such loading leads to diminished bone formation relative to bone resorption, resulting in osteoporosis. Thus, skeletal muscle not only maintains structural integrity but also regulates bone mineralization via mechanical stress [14]. Experimental evidence supports a role of HA in improving bone density. In an ovariectomized rat model, subcutaneous injection of HA at 1 mg/kg for 12 weeks increased femoral BMD by 13.6%, accompanied by elevated trabecular number (Tb.N) and reduced trabecular separation (Tb.Sp). In a clinical study, postmenopausal women receiving oral HA supplementation (200 mg/day) for 6 months exhibited a 2.1% increase in hip BMD.

4. Hyaluronic acid and exercise-induced muscle injury

4.1. Mechanisms of exercise-induced muscle injury

Exercise-induced muscle injury is a multifactorial and multistage process involving mechanical disruption, metabolic imbalance, and inflammatory responses. Initial mechanical trauma, such as overstretching or high-intensity eccentric contraction, triggers local damage to muscle fibers and the extracellular matrix (ECM). This is followed by metabolic disturbances, including mitochondrial dysfunction and oxidative stress, which further compromise cellular homeostasis. Finally, activation of inflammatory cascades exacerbates tissue damage, leading to transient impairment of muscle structure and function.

4.2. Anti-inflammatory effects of HA on skeletal muscle

Physical Barrier and Lubrication: High molecular weight HA (HMWHA, >1500 kDa) can rapidly restore the viscoelasticity of the extracellular matrix (ECM), reducing friction within the fascial layers or joint cavities, thereby minimizing secondary damage and inflammation triggered by mechanical stress [15].

Receptor-Mediated Anti-Inflammatory Signaling: HA binds to receptors such as CD44 and TLR-4, inhibiting the NF-κB, PI3K/Akt, and JAK/STAT pathways, and downregulating pro-inflammatory factors including IL-1β, TNF-α, and COX-2 [16].

Many biological effects of HA depend on the molecular size of the ligand (Fig. 1). Native HA is synthesized by hyaluronan synthases (HAS) as long polymers ranging from low to high molecular weight, up to 5 × 10^6 kDa. Hyaluronidase-1 (Hyal-1) and hyaluronidase-2 (Hyal-2) degrade HA by fragmenting the polymer from both ends toward the center, reducing molecular weight and generating HA oligosaccharides in synovial fluid. Several studies have shown significant differences between the intrinsic properties of HMWHA and short-chain HA oligosaccharides. It has been suggested that long HA polymers exhibit anti-inflammatory effects, whereas short HA oligosaccharides act as ligands to induce pro-inflammatory responses through receptor-mediated signaling. Therefore, the molecular weight distribution of HA products is critical, as a broad

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distribution with a lower average molecular weight may contain short oligosaccharide fragments [16].

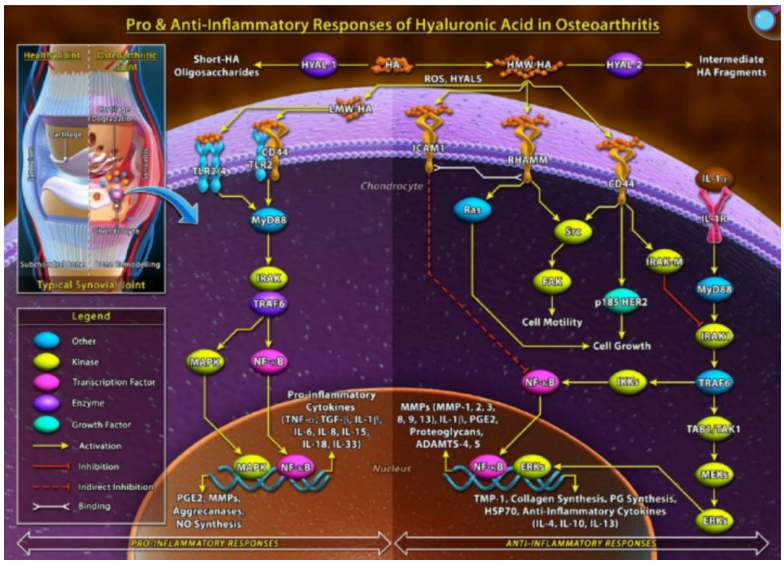

Figure 2. Pro- and anti-inflammatory roles of HA in osteoarthritis

HA therapy provides symptomatic relief through multiple mechanisms, including inhibition of receptor-mediated signaling that suppresses pro-inflammatory cytokines and chemokines, as well as promotion of anti-inflammatory mediator synthesis. Owing to its favorable biomechanical properties and low immunogenicity, HA has been approved by the U.S. Food and Drug Administration (FDA) for soft tissue applications [17,18].

Neuroregulation and Analgesia: HA can directly act on peripheral nociceptors, reducing C-fiber excitability and the release of pain mediators, thereby alleviating the vicious cycle of "inflammation–pain–muscle inhibition."

4.3. HA in muscle repair

High-viscoelastic HA (>1000 kDa) rapidly fills inter-fiber gaps, restoring ECM mechanical tension and preventing further sarcomere rupture following injury. Simultaneously, it "anchors" muscle stem cells (MuSCs) within the local microenvironment, reducing cell death caused by mechanical shear stress and supporting tissue regeneration.

5. Conclusion

Hyaluronic acid (HA) is a linear polysaccharide composed of alternating units of glucuronic acid and N-acetylglucosamine, widely distributed in the skin, synovial fluid, vitreous body, and the extracellular matrix (ECM) of skeletal muscle. Owing to its excellent water-retention capacity and viscoelasticity, HA plays a central role in tissue lubrication, as well as in the regulation of cell migration, proliferation, and differentiation. Currently, clinical and basic research on HA has primarily focused on three areas: skin hydration and anti-aging, supplementation of joint viscoelasticity, and wound repair.

The efficacy of HA in classical applications such as moisturization and joint lubrication is supported by relatively robust evidence-based medical data. However, research on its role in

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maintaining skeletal and skeletal muscle homeostasis, promoting injury repair, and enhancing function remains scattered and lacks consensus.

References

[1] Su, C., Zhang, Y., Su, L., et al. (2025). Expression changes of concave protein 1 in rats with type II diabetes and osteoarthritis. Chinese Journal of Orthopaedics, 1–6. https: //doi.org/10.20184/j.cnki.Issn1005-8478.110703

[2] Ma, X., Ma, W., Li, X., et al. (2025). Research progress of hyaluronic acid in cartilage injury repair. Journal of Lanzhou University (Medical Edition), 1–11. https: //link.cnki.net/urlid/62.1194.R.20250220.1540.005

[3] Derwich, M., Mitus-Kenig, M., & Pawlowska, E. (2021). Mechanisms of action and efficacy of hyaluronic acid, corticosteroids, and platelet-rich plasma in the treatment of temporomandibular joint osteoarthritis: A systematic review. International Journal of Molecular Sciences, 22(14), 7405.

[4] Wang, R., & Zhang, L. (2025). Research progress of traditional Chinese medicine intervention in cartilage metabolism of knee osteoarthritis. Chinese Medicine Information, 1–5. http: //kns.cnki.net/kcms/detail/23.1194.R.20250715.0932.002.html

[5] Langdahl, B. L. (2021). Overview of treatment approaches to osteoporosis. British Journal of Pharmacology, 178(9), 1891–1906.

[6] Kostenuk, P. J., Binkley, N., & Anderson, P. A. (2023). Advances in osteoporosis therapy: Focus on anabolic agents, secondary fracture prevention, and perioperative bone health. Current Osteoporosis Reports, 21(4), 386–400.

[7] Luo, C., Qin, S., Wang, Q., et al. (2023). Cost-effectiveness analysis of five drugs for treating postmenopausal women in the United States with osteoporosis and very high fracture risk. Journal of Endocrinological Investigation, 46(2), 367–379.

[8] Gu, H., Wang, J., & Deng, X. (2023). Expression and clinical significance of sFRP4 and DKK1 in serum of patients with primary osteoporosis. Hebei Medical Journal, 29(6), 922–927.

[9] Maffi, M., & Gut, M. (2023). Radiofrequency echographic multispectrometry and machine learning: One-year in review. Clinical and Experimental Rheumatology, 41(7), 1377–1383.

[10] Salarin, D., Darvishin, B., Bartinay, A., et al. (2021). Global prevalence of osteoporosis among older adults: A comprehensive systematic review and meta-analysis. Journal of Orthopaedic Surgery and Research, 16(1), 669.

[11] Zhao, F., Deng, W., Ding, J., et al. (2015). Changes in serum bone metabolism markers in osteoarthritis. Journal of Xinjiang Medical University, 38(12), 1492–1495.

[12] Du, Z., Xi, L., & Zhang, H. (2024). Clinical study on arthroscopic debridement combined with sodium hyaluronate improving bone metabolism and knee function in patients with knee osteoarthritis. Chinese Journal of Clinical and Basic Orthopaedics, 14(5), 353–357.

[13] Lv, K., Lei, W., Ma, J., et al. (2018). Effects of arthroscopic debridement combined with triamcinolone and sodium hyaluronate intra-articular injection on serum bone metabolism-related indicators in knee osteoarthritis. Journal of Guangxi Medical University, 35(10), 1392–1396. https: //doi.org/10.16190/j.cnki.45-1211/r.2018.10.016

[14] Li, J., Wang, H., Wang, Y., et al. (2014). Arthroscopic debridement combined with traditional Chinese medicine treatment for osteoarthritis. Chinese Journal of Orthopaedics, 22(8), 763–764.

[15] Iaconisi GN, Gallo N, Caforio L, Ricci V, Fiermonte G, Della Tommasa S, Bernetti A, Dolce V, Farì G, Capobianco L. Clinical and Biochemical Implications of Hyaluronic Acid in Musculoskeletal Rehabilitation: A Comprehensive Review. J Pers Med. 2023 Nov 26; 13(12): 1647. doi: 10.3390/jpm13121647. PMID: 38138874; PMCID: PMC10744407.

[16] Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P. Anti-Inflammatory Effects of Intra-Articular Hyaluronic Acid: A Systematic Review. Cartilage. 2019 Jan; 10(1): 43-52. doi: 10.1177/1947603517749919. Epub 2018 Feb 11. PMID: 29429372; PMCID: PMC6376563.

[17] Kim JJ, Kwak TI, Jeon BG, Cheon J, Moon DG. Effects of glans penis augmentation using hyaluronic acid gel for premature ejaculation. Int J Impot Res. 2004 Dec; 16(6): 547-51. doi: 10.1038/sj.ijir.3901226. PMID: 15057258.

[18] Yang DY,Ko K,Lee SH,et al. Efficacy and safety of a newly developed polylactic acid microsphere as an injectable bulking agent for penile augmentation: 18-months follow-up[J]. Int J Impot Res,2017,29(4) : 136-141.