Review

Pathophysiological and Therapeutic Roles of Fascial Hyaluronan in Obesity-Related Myofascial Disease

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Abstract: Myofascial disease is an important complication associated with obesity and one of the leading causes of physical disability globally. In the face of limited treatment options, the burden of myofascial disorders is predicted to increase along with the escalating prevalence of obesity. Several pathological processes in obesity contribute to modifications in fascial extracellular matrix mechanical and biological properties and functions. Changes in adipose tissue metabolism, chronic inflammatory phenotype, oxidative stress, and other mechanisms in obesity may alter the physiochemical and biomechanical properties of fascial hyaluronan. Understanding the pathophysiological importance of hyaluronan and other components of the fascial connective tissue matrix in obesity may shed light on the etiology of associated myofascial disorders and inform treatment strategies. Given its unique and favorable pharmacological properties, hyaluronan has found a broad range of clinical applications, notably in orthopedic conditions such as osteoarthritis and tendinopathies, which share important pathophysiological mechanisms implicated in myofascial diseases. However, while existing clinical studies uniformly affirm the therapeutic value of hyaluronan in myofascial disorders, more extensive studies in broader pharmacological and clinical contexts are needed to firmly validate its therapeutic adaptation.

Keywords: Fascia; obesity; hyaluronan; fasciopathy; myofascial disease; pathophysiology; therapeutics

1. Introduction

The Fascia Research Society, through its Fascia Nomenclature Committee, has proposed both anatomical and functional definitions of the fascia. Morphologically, a fascia was defined as “a sheath, a sheet, or any other dissectible aggregations of connective tissue that forms beneath the skin to attach, enclose, and separate muscles and other internal organs”. Functionally, the fascial system was defined as “the three-dimensional continuum of soft, collagen-containing, loose and dense fibrous connective tissues that permeate the body, providing an environment that enables all body systems to operate in an integrated manner” [1–3]. Based on histological properties and anatomical relationships, fascia may be classified into four types: superficial (subcutaneous) fascia, deep/muscular fasciae (aponeurotic and epimysial fasciae), visceral fasciae, and neural fasciae (meningeal layers and connective tissue sheath of peripheral nerves) [4,5]. Structurally the fascia tissue consists of various cell types (fibroblasts, myofibroblasts, fasciacytes, and telocytes), an extracellular matrix consisting of fibrous (types I and III collagen fibers, elastin, and fibrillin), and aqueous (water and complex mixture of glycosaminoglycans) components, and nerve elements (free nerve endings and mechanoreceptors) [4,6].

While the biomechanical properties of the clinically important fascia, such as the plantar fascia, have been well-studied [7–10], the microscopic anatomy and pathology of the fascia have received limited attention. Little is known about the elastic fiber composition, extracellular matrix characteristics, vascularity, innervation extent of the fascia tissue, and their role in disease and therapeutics [11]. Deepening our understanding of the microanatomical and biochemical basis of fascial disease in obesity may provide novel...
therapeutic insights for the medical and surgical treatment of obesity-related myofascial complications. A significant body of evidence has highlighted the critical role of fascial cells, extracellular matrix, and nerve elements in the pathogenesis of myofascial disease [4,6]. In this regard, a therapeutically relevant consideration is the role of hyaluronan (hyaluronic acid) in clinical fasciopathy. The present review aims to examine the current evidence on the pathological role and therapeutic potential of fascial hyaluronan in obesity-related myofascial disorders.

2. Hyaluronan Biochemistry, Cellular Synthesis, and Homeostasis

Despite being first described nearly 90 years ago, the role of hyaluronan in fascia physiology and pathology has only received focal attention in recent decades [12,13]. Hyaluronan is the dominant polysaccharide of the extracellular matrix of connective tissues with high cross-species structural homology, being structurally identical in bacteria and vertebrates [14]. It can be found in connective, epithelial, and neural tissues, where it provides mechanical stability and acts as a water reservoir, lubricant, and extracellular matrix homeostatic regulator [15]. Besides fascial hyaluronan, other body tissues such as the skin, tendon sheaths, pleura, pericardium, synovial fluid, the vitreous body, and the umbilical cord are also rich in hyaluronan. A 70-kg body has 15 g of hyaluronan, and about 50% of total body hyaluronan is located in the dermis [14,16].

Hyaluronan is a linear non-sulfated glycosaminoglycan composed of a single polysaccharide chain built by repeated disaccharide units of N-acetyl-D-glucosamine and D-glucuronic acid, respectively linked by β1–3 and β1–4 glycosidic bonds [12]. It is synthesized by three plasma membrane-bound hyaluronan synthases (HAS1, HAS2, and HAS3). As hyaluronan is synthesized in the plasma membrane rather than the Golgi, it lacks peptides in its fundamental structure, unlike other glycosaminoglycans [17]. Hyaluronan may be found in tissues in three forms: attached to plasma membranes, aggregated with other organic molecules, or as unbound polysaccharides [17]. Hyaluronan can interact with several extracellular matrix-binding proteins, such as aggrecans, but when not coupled to other molecules, it forms a viscous environment by self-associating and binding to water molecules [18]. In vivo, hyaluronan polymers range in size from 5000 to 20,000,000 Da and are divided into high and low molecular weight hyaluronan, each having different functional properties [19]. While high-molecular-weight hyaluronan contributes to tissue homeostasis by inhibiting cell proliferation, migration, angiogenesis, inflammation, and immunogenicity, hyaluronan oligomers have been shown to stimulate endothelial proliferation and migration, including tumor cell motility via their interaction with cluster determinant 44 (CD44) receptors, which is currently thought to be the major hyaluronan receptor on most cell types [20–22]. The membrane-bound CD44 regulates adhesion, motility, and intracellular signaling, while the receptor for hyaluronan-mediated motility (RHAMM) modulates intracellular signaling [23]. RHAMM is a centrosome- and microtubule-associated protein that is highly expressed before and during mitosis and hence prominent in neoplastic and other hyperproliferative tissues [24]. Besides the widely distributed CD44, hyaluronan fragments may also activate RHAMM, LYVE-1 (lymphatic vessel endothelial hyaluronan receptor), HARE (hyaluronan-receptor for endocytosis), ICAM-1 (intercellular adhesion molecule 1), layilin, Toll-like receptor 4, and other cell surface receptors which modulate gene expression via signaling pathways [23,25]. Accordingly, hyaluronan binding is critical for morphogenesis, matrix organization, wound repair/regeneration, inflammation, and metastasis [23].

While the predominant cell type in the fascia is the fibroblast which plays critical roles in mechanotransduction and synthesis of extracellular matrix precursors, a new class of previously undescribed cells termed “fasciacytes”, which are modified fibroblast-like cells located at the border of the different fascial layers, have been proposed as the site of fascial hyaluronan synthesis and secretion [4,26]. These cells are termed synoviocytes in the joints and hyalocytes in the eye, where they respectively secrete the hyaluronan of the synovial and vitreous fluids. Fasciacytes stain prominently with Alcian blue and are visualized as
small clusters of rounded cells with circular nuclei, perinuclear cytoplasm, and small, less-elongated cellular processes [26]. They have been shown to express hyaluronan synthase 2 mRNA and are positive for the fibroblast marker vimentin, and negative for anti-CD68 indicating they are non-derivatives of the monocyte/macrophage lineage [26,27]. The deep muscular fascia expresses high levels of hyaluronan in the interface between the fascia and the epimysium [28]. This layer of hyaluronan-rich loose connective tissue between the deep fascia and the underlying skeletal muscle was also demonstrated by Stecco and colleagues using a combination of histological and sonographic analysis [29]. Hyaluronan has been shown to facilitate the gliding between different fascial sublayers and between fascia and muscle [28,30]. Given the evidence on its endomysial histolocalisation, it has also been suggested that hyaluronan not only lubricates but promotes muscle fiber motility [31].

Proteoglycans/glycosaminoglycans, elastin, fibronectin, laminin, and numerous other glycoproteins make up the thick dynamic extracellular matrix surrounding all fascia cells [4]. Fascia homeostasis is the outcome of dynamic interactions between cellular components and the extracellular matrix, and reciprocally, small extracellular matrix functional and structural changes contribute to complex cellular adaption mechanisms [32]. Additionally, the extracellular matrix functions as a molecular storage system, capturing and releasing physiologically active chemicals that govern cellular and tissue function, development, regeneration, and repair [33]. The mechanical properties of hyaluronan are determined by its molecular weight, tissue concentration, pH, covalent modifications, alterations in binding interactions with other molecules, and fluid dynamics [30,34]. The tissue half-life of hyaluronan ranges from a few hours to several days, and removal occurs by receptor-mediated endocytosis and lysosomal breakdown with subsequent elimination via lymph nodes, liver, and kidney [17,18]. Tissue hyaluronan equilibrium is maintained by both hyaluronan synthases and the cleavage enzymes, hyaluronidases (HYAL 1, 2, and 3), as well as non-enzymatic degradation via thermal or shear stress, acidic/alkaline hydrolysis, and reactive oxygen species [14,34]. Tissue volume, viscosity, and elasticity are all affected when hyaluronan mass or molecular weight decreases due to degradation or a decline in synthesis [18].

Healthy fascia requires a specific level of the lubricating layer of hyaluronan, which allows sliding between fascial sublayers and between fasciae and adjacent structures [35,36]. The hyaluronan composition of human fascial samples obtained from different anatomic regions was first quantified by Fede and colleagues in 2018 [36]. They demonstrated that hyaluronan concentration varies in accordance with the degree of fascial plane sliding and gliding functions in different anatomic regions. For example, the average hyaluronan concentration in the retinacula of the ankle (fascia associated with a mobile joint) was 90 µg/g of fascial tissue, in contrast to the fascia adherent to a muscle (epimysial fascia), with limited lubrication requirement, such as fascia overlying the trapezius and deltoid, which had an average hyaluronan content of 6 µg/g of fascial tissue [36].

3. Obesity and Myofascial Disease

The global prevalence of obesity has escalated to pandemic proportions over the past half-century [37–39], with recent data from the World Health Organization revealing that the condition affects 13% of the world’s population [40]. A recent estimate of the economic impact of obesity in eight countries reported that the condition costs between 0.8% and 2.4% of gross domestic product (GDP) and that the magnitude of economic impact was similarly substantial in both low-, middle-, and high-income countries, and projected to increase if current trends persist [41]. The rising global trend of obesity is associated with the increasing prevalence of cardiometabolic disorders such as type 2 diabetes mellitus and hypertension, as well as a broad spectrum of orthopedic morbidities [42,43]. A growing body of evidence suggests that the histological and biomolecular changes of the human fascia contribute to several myofascial and other connective tissue disorders associated with obesity and metabolic syndrome, including adhesive capsulitis, Dupuytren’s contracture,
crystal-induced arthritis, plantar fasciitis, plantar fascia rupture, plantar fibromatosis, plantar xanthoma, and enthesopathy [12,29,43,44].

Myofascial pain syndromes are musculoskeletal pain disorders with a commonly associated neuropathic component and represent a leading cause of physical disability globally. They are thought to originate from myofascial trigger points, which are palpable hyperirritable painful spots involving a select number of muscle fibers, and may be acute or chronic, primary, or secondary to another comorbidity [45]. It was long assumed that the syndrome exclusively involved muscles, but current research suggests that the fascia plays a critical role, although the exact mechanisms and therapeutic significance of fascial pathophysiological roles remain an open subject for further investigation [46]. Pathological degenerative changes in the fascia, or fasciitis, are among the leading causes of functionally limiting musculoskeletal pain syndromes. For example, plantar fasciitis affects one in ten people in their lifetime and accounts for 1% of all orthopedic consultations [47]. A high prevalence of myofascial pain (high proportion of latent and active myofascial trigger points) is similarly reported in patients presenting with chronic back pain, non-specific neck pain, and chronic non-traumatic shoulder pain [48–51]. The prevalence of myofascial pain ranges from 21–93% in general orthopedic practice and specialist pain clinic patients, respectively, and up to 85% of people in the general population will experience myofascial pain in their lifetime [52]. In the United States alone, the national economic burden of plantar fasciitis was estimated at 284 million US dollars, with medication costs accounting for about 80% of total costs [53]. Several risk factors have been identified, including obesity, traumatic musculoskeletal injuries, spine disease, cumulative and repeated strain, postural dysfunction, and physical deconditioning [45].

Obesity is a key epidemiological risk factor for myofascial disease [54–60]. A systematic review of 51 studies found that the only significant predictor related to plantar fasciitis was a body mass index (BMI) >27 kg/m² [61]. Even in an active population such as recreational and competitive runners, of eleven analyzed risk factors, increased BMI and body mass were found to be primary risk factors for fasciopathy [55]. In recent-onset type 2 diabetic subjects without complications, plantar fascia thickness was increased compared to the controls and significantly associated with adiposity and BMI values, suggesting important clinical implications in obese diabetic patients [62]. Plantar fascia thickness has also been shown to be a reliable alternative index of tissue glycation and a significant predictor of microvasculopathy, an essential denominator in several obesity-related complications [63–67]. Cytokines and other inflammatory molecules that have been demonstrated in the environment of myofascial trigger points are also typically overexpressed in the skeletal muscle of obese patients [68,69]. High-fat diet-induced obese mice were shown to express elevated spontaneous neurotransmission, which facilitates the development of myofascial trigger points [60].

4. Pathophysiological Importance and Associated Alterations of Hyaluronan in Obesity

Hyaluronan dysregulation has been implicated in the pathophysiology of several clinical conditions, including cancer, diabetes, autoimmune disease, and vascular disease [70–76]. Similarly, hyaluronan-mediated signaling is disrupted in various tissues in obesity. In metabolic comorbidities associated with obesity, such as nonalcoholic hepatic steatosis and insulin resistance, elevated circulatory levels of hyaluronan have been demonstrated and suggested to have diagnostic value [77–80].

Hyaluronan binds to cell-surface proteins, including receptors, to exert a broad range of biological effects on adipose tissue. Increasing evidence points to the involvement of hyaluronan and its receptors in obesity-related adipocyte hyperplasia and hypertrophy and adipose tissue metabolism [81]. An enhanced expression of hyaluronan synthase-1 was demonstrated in adipose tissue from obese patients [82]. It has been suggested that adipocyte hypertrophy contributes to adipose tissue inflammation [83]. Adipose tissue hypertrophy during obesity-related weight gain severely destabilizes extracellular matrix
homeostasis by modifying the local oxygen supply, which in turn triggers cellular stress events and inflammation [82]. A potential role of hyaluronan in adipogenesis in vivo has been demonstrated in mouse models of high-fat diet-induced obesity [79,84–87]. Hyaluronan levels were noted to be increased in these mice, mediating insulin resistance via CD44-dependent mechanisms. Treatment with exogenous hyaluronidase was found to dose-dependently decrease fat mass and adipocyte size and inhibit abdominal, muscular, and hepatic lipid accumulation, consequently increasing insulin sensitivity [84–86].

The accumulation and turnover of hyaluronan polymers in many cell types have been linked to inflammation. The role of hyaluronan in regulating inflammatory responses, including the expression of inflammatory genes, the recruitment of inflammatory cells, and the production of inflammatory cytokines, is now firmly established [88]. Hyaluronan modulates the cellular proliferative phase of tissue repair following inflammatory damage by facilitating fibroblast detachment from the extracellular matrix, mitosis, and cell migration via CD44 and RHAMM interactions [89–91]. Human and animal inflammatory disorders such as sarcoidosis, idiopathic pulmonary fibrosis, farmer’s lung, graft rejection, experimental myocarditis, myocardial infarction, and inflammatory bowel disease are associated with increased hyaluronan levels in tissues [92]. As previously noted, high-molecular-weight hyaluronan is anti-inflammatory and immunosuppressive, while low-molecular-weight hyaluronan is pro-inflammatory [21,22].

It was shown that while total plasma hyaluronan molecules remain unaltered, the circulating level of low-molecular-weight hyaluronan fragments is elevated in obesity and may play a key role via Toll-like receptor (TLR)-mediated activation of innate immune cells in activating low-grade inflammatory phenotypes and other metabolic complications [82,93]. The expression of hyaluronan receptors in leukocytes is altered in obesity, with consequent alterations in the inflammatory response of leukocytes to low-molecular-weight hyaluronan. It was shown that low-molecular-weight hyaluronan induces nuclear factor kappa B (NF-κB)-dependent activation in peripheral blood monocytes and THP-1 monocytes, leading to an increase in pro-inflammatory markers [82]. Hyaluronan increases tumor necrosis factor-α (TNF-α), insulin-like growth factor-1 (IGF-1) mRNA transcript expression and protein synthesis, interleukin 1 beta (IL-1β), and interleukin 8 (IL-8) via a CD44-mediated mechanism and modulates cytokine-activated lymphocyte adhesion to the endothelium [94,95]. TNF-α may also trigger the release of the hyaluronan-binding protein, TSG-6 (TNFα-stimulated gene-6 protein), which propagates the inflammatory response [96], while IL-1β up-regulates hyaluronan synthase-1 gene expression in adipose tissue [82].

The inflammatory milieu in obesity underlies the pathophysiology of several associated complications, including the development of fasciopathies and tendinopathies [97–101]. The array of proinflammatory mediators, such as cytokines, adipokines (e.g., leptins), lipocalin-1, serum amyloid A-3, and adiponectin released during the development of obesity-related chronic inflammatory phenotypes promote insulin resistance by altering the extracellular matrix, the capillary network architecture, and the glucose uptake mechanisms [102]. The resulting hyperglycemia causes changes in the stiffness, gliding, and distribution of force transmission in the fasciae due to collagen thickening, elastic fiber fragmentation, and changes in glycosaminoglycans, particularly hyaluronan, with cascading ramifications at the cellular and molecular levels, including alterations in cellular proliferation, differentiation, growth, and migration [4]. In addition, inflammation increases reactive oxygen species, which degrade collagen, laminin, and hyaluronan, and hyaluronan fragments generated by this process sustain an inflammatory cycle (recruitment of leukocytes and release of various inflammatory mediators such as reactive oxygen species, cytokines, chemokines, and destructive enzymes) [14,88]. Conversely, high molecular weight hyaluronan works as an effective barrier to the inflammatory process and protects against oxidative damage by free radicals (superoxide anions, hydroxyl radicals, and hypochlorite) [103].
5. The Etiological Significance of Changes in Hyaluronan Properties in Myofascial Disease

The fibrous and glycosaminoglycan components of the fascial extracellular matrix can be affected by various physical, mechanical, hormonal, and pharmacological factors [4]. Alterations in the physiological levels of hyaluronan have been demonstrated to be etiologically important in myofascial pain syndromes [29,36]. Changes in the physical and chemical properties of hyaluronan are associated with modifications in extracellular matrix viscoelasticity, mechanical plasticity, and nonlinear elasticity [104,105], all of which may contribute to myofascial disease (Figure 1). Although the evidence is conflicting, it has been suggested that a strong association exists between body temperature and obesity markers [106]. With increasing temperature, both stiffening and weakening of hyaluronan-based hydrogels were observed [107,108]. Given that pH is directly related to viscosity [109], the biomechanical properties of hyaluronan may be altered by tissue acidity from increased lactic acid accumulation seen in obesity [110]. It was shown that hyaluronan degradation occurs at pH < 4 and pH > 11 [111]. Alterations in hyaluronan function may result from the effects of van der Waals and hydrophobic forces on its concentration, polyelectrolyte properties, and aggregation characteristics [25,108]. Hyaluronan takes on non-Newtonian characteristics and becomes more viscous at higher concentrations [112]. Myofascial disorders may originate from altered hydrodynamic characteristics and atypical viscoelastic properties of fascia [46]. Obesity is associated with diminished physical mobility [113,114], which has been shown to raise the concentration of hyaluronan without adequate hyaluronan recycling, increase hyaluronan viscosity, and limit the lubrication and gliding of the layers of connective tissue and muscle, with a consequent increase in overall fascial thickness, stiffness, and pain perception [30]. Any loading condition reduces hyaluronan viscosity; however, resting conditions allow hyaluronan to recover to a more viscous state. The distribution of lines of force inside the fascia alters when hyaluronan changes from lubricating to adhesive function, a process referred to as densification of fascia [115,116]. As the connective tissue and its extracellular matrix thicken and become denser, the capacity of fascial tissue to slide is reduced or eliminated [116,117]. Chronic densification modifies the gliding of the fibrous layers, influencing collagen fiber deposition locally and remotely [116]. While fascial densification and fibrosis describe alterations in the fascia resulting in myofascial pain syndromes, it is important to differentiate both processes as they have distinct pathological and therapeutic implications. Densification indicates a potentially easily reversible modification in the loose connective tissue due to hyaluronan super-aggregation with a decreased water-binding capacity resulting in altered mechanical characteristics of the fascia but not its overall structure, whereas fibrosis refers to a difficult-to-reverse modification of the general tissue structure and mechanical properties from the excessive deposition of fibrous connective tissue as part of a reparative or reactive response [25,116]. The loose connective tissue found within the deep fascia can be altered by diet, exercise, and overuse syndromes, resulting in fascial densification, whereas trauma, surgery, and diabetes can modify the fibrous layers of the deep fasciae, resulting in fibrosis of the fascia [116]. Chronic, nonspecific neck pain may be reflective of fascial densification, whereas Dupuytren’s disease and eosinophil fasciitis are typical fibrotic disorders, and therapeutic approaches are distinct in both pathologies [46,118]. Studies have demonstrated that mechanosensitive signaling underlies obesity-induced connective tissue fibrosis [119]. Fascial tissues contain various types of mechanoreceptors, in addition to the vast network of free nerve endings that play important roles in pain perception and regulation [120,121]. Myofibroblasts in the fascia, which are specialized fibroblasts with contractile properties that regulate the tissue basal tone, are also etiologically important in some pathological fibrotic contractures such as Dupuytren disease that affects the palmar and digital fascia of the hand [4].
Figure 1. Relationships of pathophysiological mechanisms in obesity with changes in hyaluronan properties and the development of myofascial disease. ECM: extracellular matrix; HAS1: hyaluronan synthase 1; ROS: reactive oxygen species.

6. Therapeutic Considerations of Hyaluronan in Myofascial Disease

The complicated peripheral and central pathophysiological mechanisms in myofascial pain syndromes present unique challenges for effective treatment. Current pharmacological therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics (e.g., tramadol), muscle relaxants (e.g., tizanidine, cyclobenzaprine), anticonvulsants (e.g., gabapentin and pregabalin), antidepressants (e.g., tricyclic antidepressants such as...
amitriptyline and serotonin-norepinephrine reuptake inhibitors such as duloxetine), benzodiazepines, tropisetron (5-HT$_3$ receptor antagonist and alpha-7-nicotinic receptor agonist), sumatriptan (peripheral 5-HT receptor agonist), lidocaine transdermal patch, intramuscular ketamine, steroid injections, and botulinum type A toxin (BoNT-A) injections. Several non-pharmacological treatment modalities have also been proposed, including manual therapy, dry needling, ultrasound therapy, ischemic compression, phonophoresis, pressure release, transcutaneous electric nerve stimulation (TENS), electrical twitch obtaining intramuscular stimulation (ETOIMS), magnetic stimulation, and laser therapy [52,122–126]. Unfortunately, the current pharmacological and non-pharmacological treatment modalities are not backed by high-quality evidence regarding efficacy and safety, and the search for evidence-based effective treatment options continues.

Unraveling novel therapeutic approaches to alleviate chronic pain syndromes may be facilitated by an enhanced understanding of the pathophysiological importance of hyaluronan and other components of the connective tissue matrix of fascia, as well as the mechanical forces that are both permitted and restricted by fascial planes [116]. Hyaluronan’s ubiquitous availability, complete resorbability, biocompatibility, hydrophilicity, unique viscoelasticity, and minimal immunogenicity and adverse effects account for its wide biomedical and clinical applications in different fields of medicine (e.g., viscosupplementation for osteoarthritis treatment, vitreous substitution/replacement in ophthalmic surgery, as dermatological fillers, as scaffolds in nerve-, vessel-, and adipose tissue-engineering, as drug conjugation and delivery agent, and as an immunomodulatory agent in cancer therapeutics) [14,18,127–129]. Cosmetic injection of hyaluronan as a dermal filler (an FDA-approved clinical use) was ranked as the second and third most common non-surgical procedure for women and males, respectively [130,131]. Intra-synovial injection of crosslinked and non-crosslinked hyaluronan as viscosupplements is also a favored and FDA-approved treatment for osteoarthritic pain [132–134].

Several preclinical and clinical studies have reported on the therapeutic applications of hyaluronan in managing fasciopathies, tendinopathies, and osteoarthritis, all of which share important pathophysiological mechanisms [18,135–146]. In an animal model of osteoarthritis, administration of hyaluronan to isolated medial articular nerves dramatically lowered both ongoing and movement-evoked nerve activities, indicating a therapeutically important antinociceptive activity in inflamed joints through an elastoviscous, rheological effect on nociceptive afferent fibers [147]. In vitro experiments have demonstrated therapeutically important effects of hyaluronan on the extracellular matrix in osteoarthritis, including increased synthesis of chondroitin sulfate and proteoglycans, suppressed proteoglycan release from chondrocyte, and cartilage cell-matrix, and inhibited proteoglycan breakdown from cartilage. Several effects of hyaluronan on inflammatory mediators and immune cells have been described, notably decreased levels of IL-1-induced prostaglandin E$_2$, TNF-α, plasminogen activator activity, increased tissue inhibitor of metalloproteinases-1, enhanced antioxidant effects, reduced lymphocyte stimulation, motility, and proliferation, suppressed neutrophil aggregation and adhesion, inhibited macrophage and neutrophil phagocytosis, and enhanced polymorphonuclear leukocyte phagocytosis, adherence, and migration [148]. These effects of hyaluronan on the extracellular matrix, inflammatory mediators, and immune cells are therapeutically important in fascial disease and support the adaptability of hyaluronan for the treatment of myofascial disorders. As in osteoarthritis, functionally limited patients with myofascial disease who have not responded adequately to conventional pharmacological and nonpharmacological treatment options, those who have gastrointestinal or renal intolerance to NSAIDs and other therapies, and those who wish to postpone or are ineligible for surgery are good candidates for hyaluronan treatment [132]. On the other hand, it has been suggested that obesity may be an independent risk factor for viscosupplementation failure in patients with osteoarthritis [149], although further investigation demonstrated that benefits were similar in normal-weight and obese patients with mild or moderate knee osteoarthritis who responded to treatment [150].
Indeed, a potential therapeutic role of hyaluronan injections in treating fasciopathies has been demonstrated [151]. A recent randomized controlled trial found that the administration of five injections of high-molecular-weight hyaluronan is a safe and effective treatment option for patients with persistent pain for more than 12 weeks from plantar fasciopathy [152]. In patients with various enthesopathies (lateral epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy, and plantar fasciitis), a single injection of up to 2.5 mL hyaluronan uniformly reduced pain as assessed by the visual analog scale (VAS) for pain and local pain symptoms 1 week after injection [145]. Tendinopathies and fasciopathies share similar pathophysiological mechanisms, mindful that tendons are technically part of the fascial system. Recall that the broader functional definition of the fascial system incorporates elements such as adipose tissue, adventitiae and neurovascular sheaths, aponeuroses, deep and superficial fasciae, epineurium, joint capsules, ligaments, membranes, meninges, myofascial expansions, periosteum, retinacula, septa, tendons, and visceral fasciae [1].

A few studies have compared hyaluronan and other conventional therapies, as well as different pharmacological preparations and modifications of hyaluronan. Raeissadat et al. found that while corticosteroid injection appeared to have a faster trend of improvement in the short term, hyaluronan injection was comparably effective in reducing the symptoms of plantar fasciitis [144]. Additionally, hyaluronan may also be considered a physiologically more favorable option than corticosteroids which are notorious for a broad spectrum of short- and long-term adverse effects. At three months post-treatment, pain ratings indicated that two peritendinous hyaluronan injections were more effective than conventional extracorporeal shock wave therapy in treating patients with Achilles’ midportion tendinopathy for ≥ 6 weeks [153]. In patients with lateral elbow, Achilles, and patellar tendinopathy, ultrasound-guided peritendinous injections of low-molecular-weight hyaluronan (500–730 kDa) were safe, well-tolerated, and associated with significant pain improvement and reduction in ultrasound-assessed tendon thickness and neovascularization [141]. In a recent study comparing ultrasound-guided injections with low molecular weight (500–730 KDa) and high molecular weight (>2000 KDa) hyaluronan, Mohebbi et al. found that while both hyaluronan types had similar efficacy in the treatment of rotator cuff tendinopathy, patients tolerated low-molecular-weight injections better [154]. In patients with knee osteoarthritis, Bahrami et al. showed that a single high-molecular-weight hyaluronan injection is as effective as multiple injections of low-molecular-weight hyaluronan at 2- and 6-months follow-up [155]. In contrast to the native form of hyaluronan (>1000 kDa), lower-molecular-weight forms of the molecule (<500 kDa, especially preparations in 100–250 kDa) are pathophysiologically important as proinflammatory mediators [156,157]. Thus, further studies will be needed to clarify the impact of molecular weight on the therapeutic effects of hyaluronan. Furthermore, mindful that most of the current pharmacologic adaptations of hyaluronan in myofascial disease primarily aim to address the pathological consequences of the changes in its tissue concentration or molecular weight, it would be useful to explore the therapeutic endogenous or exogenous modifications of hyaluronan to target other pathophysiological mechanisms such as covalent modifications, binding interactions, rheological alterations, pH changes, and alterations in adipose tissue metabolism and inflammatory phenotype. Focal studies in obese patients with myofascial disease are also warranted to clarify the impact of obesity on the therapeutic potential of hyaluronan in myofascial disease.

Some investigators have explored molecular alterations to exogenously administered hyaluronan to change the extracellular matrix’s mechanics. Low-load elastic mechanical features, such as lower toe modulus and a tendency toward lower toe stiffness and a larger transition strain, are seen in the fascial extracellular matrix treated with tyramine-substituted high-molecular-weight hyaluronan [158]. Given its relatively short half-life in biological fluids, a number of modifications of hyaluronan molecules to extend the duration of its biological actions have been explored. The most common of these is crosslinking to form a hydrogel; however, this could lead to higher viscosity and toxicity [159]. On
the other hand, stimulating endogenous hyaluronan production has been explored as another therapeutic strategy. The endocannabinoid receptors 1 and 2 (CB1 and CB2) are expressed in various deep fasciae, and it is known that the endocannabinoid system is crucially involved in the modulation of pain, inflammation, and fibrosis [160]. For example, a synthetic cannabinoid induced a rapid production of hyaluronan and hyaluronan-rich vesicles in an in vitro culture of fascial fibroblasts, confirming a peripheral effect of the endocannabinoid system on fascial cell regulation and remodeling of the formation of the extracellular matrix [143].

A potential therapeutic role of exogenous hyaluronidases has also been suggested. Trigger point injection of hyaluronidase was reported to substantially decrease clinically assessed pain in patients with myofascial pain disorders [161]. Similarly, in patients with spastic disorders partly related to hyaluronan accumulation in muscles, hyaluronidase injections improved both passive and active mobility [162]. It is thought that the beneficial effects may be related to modifications in hyaluronan viscosity. In addition, recombinant hyaluronidase PH20 (PEGPH20) was found to significantly reduce adipose tissue mass and adipocyte size and improve insulin sensitivity in a mouse model of diet-induced obesity [79]. These effects may ameliorate the pathological ramifications of adipose tissue inflammation in myofascial disease. Finally, an understanding of the rheological properties of hyaluronan provides a physicochemical explanation of the therapeutic effects of massage, manipulation, laser therapy, and other physical therapy procedures in myofascial disease, namely the disaggregation of the pathologic chain–chain interactions of hyaluronan molecule under controlled physical conditions such as high temperature [46].

7. Conclusions

Obesity is a primary risk factor for myofascial disease, which is a leading cause of physical disability globally. With the escalating prevalence of obesity, it is expected that the burden of myofascial disease will worsen. Unfortunately, current treatment options are limited in terms of safety and efficacy, and thus new therapeutic strategies are needed. Clarifying the etiological significance of various components of the connective tissue matrix of the fascia in obesity may aid in developing novel therapeutic methods for obesity-related myofascial disorders. In particular, understanding the pathophysiological importance of fascial hyaluronan may provide valuable therapeutic insights. Hyaluronan is the dominant polysaccharide of the extracellular matrix of connective tissues, which provides mechanical stability and acts as a water reservoir and lubricant, allowing sliding between fascial sublayers and between fasciae and adjacent structures. It also acts as an extracellular matrix homeostatic regulator via various cellular mechanisms and interactions.

Alterations in the physical and chemical properties of hyaluronan are associated with modifications in extracellular matrix viscoelasticity and other mechanical properties and biological functions and have been demonstrated as critical factors in the development of myofascial disease in obesity. Understanding this pathophysiological connection paves the way for the potential therapeutic exploitation of hyaluronan. Given its ubiquitous availability and unique pharmacological properties, hyaluronan has found a broad range of clinical applications, including in orthopedic disorders such as osteoarthritis, tendinopathies, and fasciopathies. While the relatively few results of therapeutic adaptation in myofascial disease are promising and supported by the current understanding of the pathophysiological importance of hyaluronan in fasciopathy, larger and more rigorous clinical trials utilizing a broader spectrum of myofascial disorders or different modifications of hyaluronan molecule are warranted to validate its therapeutic potential.

Author Contributions: Conceptualization, C.K.U., E.C. and N.U.; writing—original draft preparation, C.K.U.; writing—review and editing, C.K.U., E.C. and N.U.; visualization, C.K.U. and N.U.; supervision, N.U. and E.C. All authors have read and agreed to the published version of the manuscript.

Funding: The authors gratefully acknowledge financial support from the Slovenian Research Agency (ARRS), Grant No. P3-0043 and N3-0256.
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