REVIEW

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The Role of DHEA, NGF, and ADAMTS5 Pathways in Osteoarthritis and Current Developments

Osteoartritte DHEA, NGF ve ADAMTS5 Yollarının Rolü ve Mevcut Gelişmeler

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Abstract

Degenerative joint disease is a condition that affects joints and is commonly referred to as osteoarthritis (OA). This form of arthritis is most prevalent among women and tends to become more frequent as people age. The pathogenesis of OA involves an imbalance of cytokines in favor of pro-inflammatory cytokines. However, the steroid hormone dehydroepiandrosterone (DHEA) exerts chondroprotective effects and regulates the balance of catabolic factors such as thrombospondin motif disintegrin and metalloproteinase (ADAMTS), thereby playing a role against OA. Pro-inflammatory cytokines induce aggrecanases, such as ADAMTS5, which degrade the extracellular matrix and contribute to OA. The molecule nerve growth factor (NGF), associated with pain in OA, is important for cartilage homeostasis, and DHEA can modulate pain by interfering with NGF receptors. This review covers the roles of DHEA, ADAMTS5, and NGF in the pathogenesis of OA, their relationship with pain pathways, and their use in current treatments. We also anticipate that these pathways will be crucial in developing new strategies to prevent and treat OA, and understanding their interactions may make it possible to enhanced the quality of life of patients with OA.

Keywords: ADAMTS5, DHEA, NGF, osteoarthritis

Öz

Dejeneratif eklem hastalığı, eklemleri etkileyen ve genellikle osteoartrit (OA) olarak adlandırılan bir durumdur. Bu artrit formu en çok kadınlar arasında görülür ve insanlar yaşlandıkça daha sık olma eğilimindedir. OA'nın patogenezi, sitokinlerin pro-enflamatuvar sitokinler lehine dengesizliğini içerir. Ancak steroid hormon dehidroepiandrosteron (DHEA) kondroprotektif etki gösterir ve trombospondin motif disintegrin ve metalloproteinaz (ADAMTS) gibi katabolik faktörlerin dengesini düzenleyerek OA'ya karşı rol oynar. Pro-enflamatuvar sitokinler, hücre dışı matrisi bozan ve OA'ya katkıda bulunan ADAMTS5 gibi agrekanazları indükler. OA'da ağrı ile ilişkili sinir büyüme faktörü (NGF) molekülü, kıkırdak homeostazı için önemlidir ve DHEA, NGF reseptörlerine müdahale ederek ağrıyı modüle edebilir. Bu derlemede OA patogenezinde DHEA, ADAMTS5 ve NGF'nin rolleri, ağrı yolakları ile ilişkileri ve güncel tedavilerdeki kullanımları ele alınmaktadır. Ayrıca, bu yolların OA'yı önlemek ve tedavi etmek için yeni stratejiler geliştirmede çok önemli olacağını ve etkileşimlerinin anlaşılmasının OA'lı hastaların yaşam kalitesini artırmayı mümkün kılacağını tahmin ediyoruz.

Anahtar kelimeler: ADAMTS5, DHEA, NGF, osteoartrit

Introduction

Worldwide, more than 250 million people are affected by osteoarthritis (OA), which is known as the most prevalent form of arthritis and characterized as a degenerative joint disease (1-3). Factors such as continued population growth and aging are the main causes of the increasing in the prevalence of OA which makes it considered as on of the

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leading causes of disability among elderly (4,5). OA has a higher incidence in women and is a significant socio-economic burden in many countries globally (6). The disease is progressive and debilitating, causing pain and resulting in a loss of function, which can be so severe that it disrupts the patient's ability to get restful sleep. At the societal level, the annual cost of OA is estimated to exceed $303 billion due to medical costs and lost earnings (7). The economic impact of OA is expected to double by 2030 on a global scale (8), emphasizing the urgency for extensive research to comprehensively understand the contributing factors in the onset and advancement of the disease. Various factors contribute to women's susceptibility to OA, including thinner cartilage, joint instability, misalignment, and unequal mechanical loading (9). Recent studies have demonstrated that a sharp decrease in sex hormone levels during menopause can trigger OA development (10,11). Other risk factors for OA include trauma, genetics, high basal metabolic index, and structural abnormalities in the joint (12). Genetic factors have been found to be effective in primary generalized OA with Heberden's nodule, Bouchard's nodule, hip involvement, and knee involvement. This is particularly evident in Heberden's nodules and is carried by an autosomal gene that is dominant in females and recessive in males. Matched twin and family-risk studies have shown that the genetic contribution to OA may be around 50-65% (13). For instance, occupational activity in professional athletes such as football players can cause the development of OA (12). OA can affect both small joints, such as those in the hand, and larger joints such as the knee and hip (14). Although pain is the primary symptom, other symptoms may accompany OA, including joint swelling, locking, cramping, decreased range of motion, and morning stiffness that resolves within thirty minutes (15). Radiographic evaluation of the joint is the gold standard in diagnosis (16). Treatment options for OA vary depending on the severity of the disease and the individual's specific needs. Some of the available treatments include joint replacement surgery, autologous mesenchymal stem cell transplantation, and non-steroidal anti-inflammatory drugs (NSAIDs) to reduce pain (17,18). In those whose pain is not adequately controlled, first-line evidence-based analgesia, NSAIDs and acetaminophen (paracetamol) are used. Oral NSAIDs and the use of cyclooxygenase-II (COX-II) inhibitors, opiates, or intra-articular steroids are considered when first-line agents fail (13,19). Additionally, early interventions such as chondroitin sulfate and glucosamine may be recommended (17). Physical therapies can also be used to treat early-stage OA (17). Finally, a Mediterranean diet may decrease the prevalence of OA and improve patients' quality of life (20).

In the pathogenesis of OA, an important factor is the disruption of the balance between anti-inflammatory and pro-inflammatory cytokines, with pro-inflammatory cytokines often becoming more dominant. The induction of interleukin (IL)-1β results in aggrecanases such as a Disintegrin and Metalloproteinase with ThromboSpondin motifs (ADAMTS)-4 and ADAMTS5 leading to extracellular matrix (ECM) degradation. Moreover, matrix metalloproteinase (MMP) induction can cause hypertrophy, differentiation, and apoptosis in chondrocytes due to these events (21). Among the 19 members of ADAMTS enzymes with various functions, ADAMTS-5 is more notable in arthritis (22). Dehydroepiandrosterone (DHEA) is a steroid hormone produced by the adrenal gland cortex, which regulates the balance between catabolic factors such as ADAMTS in cartilage (23). DHEA shows chondroprotective effects and reduces oxidative stress, protecting against OA (24). Although the role of DHEA in modulating OA-related pain is not confirmed, studies suggest that DHEA can interfere with nerve growth factor (NGF) receptors (25). NGF is primarily expressed in synovial fibroblasts and is associated with pain. Patients with knee OA and hip OA have higher NGF expression, as studies have demonstrated (26). There is evidence from mouse models that NGF and other neurotrophins are overexpressed in symptomatic diseases and are themselves synthesized by joint connective tissue (19). In 2019, a study emphasized the role of NGF signaling in the calcification of human joint chondrocytes and the importance of NGF signaling in articular cartilage homeostasis (27). Although conventional OA treatments alleviate pain, they cannot reverse cartilage damage (28). Therefore, it is crucial to further explore new molecular targets. This article will explain how ADAMTS5, DHEA, and NGF contribute to OA disease and the mechanisms they mediate by summarizing articles published in the last 5 years.

In humans, DHEA is synthesized in the central nervous system (CNS), gonads, and adrenal cortex, and it has been found to have anti-inflammatory effects on various tissues, including the prevention of leukocyte recruitment. DHEA has been shown to interact with various nuclear receptors, such as estrogen receptors, as well as G protein-coupled receptors found in endothelial and neuronal cells (29). In a study conducted by Lazaridis et al. (30), specific antibodies were employed to target tropomyosin-related kinase A (TrkA) and p75 in coimmunoprecipitation assays and

Western blot analyses of precipitates. The study showed that DHEA can directly suppress the NGF receptors p75 and TrkA, and can eliminate both receptors from PC12 cells (30). Given this discovery, it is feasible that DHEA could potentially compete with NGF for its intended receptors, resulting in the inhibition of peripheral pain production. This is because NGF binding to these receptors located in peripheral nociceptors is responsible for initiating the downstream cascade of pain signals (25,31).

In addition, research has demonstrated that both DHEA and NGF can effectively prevent apoptosis in neuronal cells. Their antiapoptotic effects begin at the plasma membrane and involve the activation of similar prosurvival kinase cascades. They also regulate the transcription of the antiapoptotic protein B-cell lymphoma 2 (Bcl-2) through the activation of transcription factors nuclear factor kappa-B (NF-B) and cyclic AMP-responsive element binding protein. Researchers have hypothesized that NGF receptors may play a role in the antiapoptotic effects of DHEA, given the similarities observed in the signal transduction pathways triggered by both molecules (32).

DHEA Pathways in OA

DHEA is a hormone that is synthesized in the zona reticularis of the adrenal gland and serves as the precursor to all sex steroid hormones. Its levels are more closely linked to age than gender, with a marked decline in the elderly that is strongly linked to the development of age-related conditions (33,34). Numerous studies have emphasized the potential therapeutic benefits of DHEA in treating chronic degenerative joint diseases, including OA. Earlier studies have suggested that administering DHEA has a positive effect on cartilage preservation in animal models of OA, particularly in the early and mid-stages of the disease (35-37). In 2015, a study was conducted to investigate the modifying effect of DHEA in various stages of experimentally induced OA disease. The results showed that DHEA treatment significantly reduced cartilage lesions and delayed cartilage degeneration in four regions of the knee (38). These findings suggest that DHEA may play a role in the pathophysiology of OA. DHEA is produced by the zona reticularis part of adrenal gland (39). The inactive sulfate ester of DHEA is converted to sulfate DHEAS in the adrenal glands and liver (40). They are bound to albumin and together form the most abundant steroid hormones in the human circulation (41). Due to the aging-related decrease of DHEAS and DHEA levels, it has been suggested that the formation of aging-related diseases may be linked to a relative deficiency of these hormones (42,43). Therefore, it is important to consider the role of DHEA in the context of OA and explore its potential as a treatment option. Moreover, DHEA has been shown to have protective effects against various aging-related diseases such as dementia (44,45), osteoporosis (46), and atherosclerosis (47).

DHEA's ability to positively influence chondrocyte/articular cartilage metabolism has been demonstrated in numerous animal- and cell-based studies, which supports its chondroprotective effects (36,37,48). Disruption to this role of DHEA could be considered as a predominant cause of OA related pathogenesis. Chondrocytes, a special cell type of the skeletal system, play a significant role in skeletal maturation and fracture healing, and endochondral ossification, a process that replaces the developing cartilage nidus by bone, may assist both fracture healing and skeletal maturation (49). Although there are few studies about the relationship between DHEA and chondrocytes, the literature suggests that DHEA can affect the overall performance of chondrocytes (49). By preventing the expression of matrix metalloproteinases enzymes known to catalyze cartilage degradation, DHEA has a chondroprotective impact on mature cartilage (36,37,48). Therefore, DHEA may be helpful in degenerative chronic conditions like OA. Moreover, there is evidence to suggest that Wnt/β-catenin pathway can be modulated by DHEA, which is critical for the maintenance of myogenic and cartilage homeostasis, with β-catenin levels playing a crucial role (50). A 2013 study examined the protective mechanism of DHEA in experimental models of OA and suggested that the chondroprotective effect of DHEA on the animals cartilage and chondrocytes may be due in part to its aromatase-mediated conversion to estrogens. This process may occur via the blocking of aromatase with letrozole (36). Therefore, it is understood that DHEA levels play a vital role in the mechanism of OA. In healthy cartilage, a robust collagen scaffold and high aggrecan content are necessary for its weight-bearing properties. However, massive loss of aggrecans, caused by aggrecanases, is the hallmark of most arthropathies, including OA (51). Aggrecanase-mediated degradation of aggrecan is an important event in the early stages of OA. While the mechanisms of action of DHEA in OA are not fully understood, data from *in vitro* studies and animal models suggest that its protective efficacy on osteoarthritic cartilage may be due to its role in the inhibition of pro-inflammatory pathways, leading to down-regulation of MMP enzymes that play a critical role in aggrecan loss in OA (37,52). Additionally, DHEA has been shown to have an anti-catabolic effect by suppressing MMPs and inducing tissue inhibitor of metalloproteinases (TIMPs), which

suggests that modulating the balance between MMPs and TIMPs is another protective mechanism of DHEA on OA (53).

Researchers conducted a study in 2003 to explore the impact of DHEA on the expression of catabolic enzymes in chondrocytes. The results demonstrated that DHEA treatment suppressed the expression and protein synthesis of MMP-1, a metalloproteinase associated with cartilage degradation, while increasing the expression and synthesis of TIMP-1, an inhibitor of MMP-1. Additionally, DHEA treatment decreased the expression of type I collagen, which is a marker of ECM senescence, and increased the expression of type II collagen, a marker for chondrogenesis (37). These findings suggest that DHEA may have chondroprotective effects in osteoarthritic chondrocytes.

In 2006, a follow-up study explored the influence of DHEA on chondrocytes obtained from neonatal rats that were exposed to catabolic stimulators, such as lipopolysaccharide (LPS) and *S*-nitroso-*N*-acetyl-l-penicillamine (SNAP). The study revealed that DHEA treatment did not impact the viability of healthy chondrocytes or interfere with their glycosaminoglycan (GAG) production capabilities (49). Furthermore, the administration of DHEA was shown to suppress the expression of prostaglandin E2 caused by LPS, MMP-13, MMP-1, and MMP-3, and also hinder the NO synthesis and GAG degradation induced by SNAP in chondrocytes (49). These results suggest that DHEA possesses anti-catabolic characteristics that address inflammation and degeneration, two crucial biological processes involved in the progression and development of OA (49). Taken together, these investigations indicate that DHEA can protect cartilage by impeding catabolic enzymes, stimulating the production of extracellular matrix, and halting inflammation and degeneration in chondrocytes. These results underscore the potential therapeutic advantages of DHEA in treating OA (53).

The pathophysiology of OA involves a complex interplay of various factors, including ECM-degrading enzymes. The MMP family has been extensively studied as an important catabolic factor in the development of OA. However, other enzymes, such as the urokinase plasminogen activator (uPA), the cysteine protease family, and the disintegrin and metalloproteinase with thrombospondin motifs family, have also been implicated in the pathogenesis of OA (54). uPA has been shown to regulate the extent of ECM degradation and is believed to play a role in the development of arthritis (54). Aggrecanases, particularly ADAMTS4 and ADAMTS5 from the ADAMTS family, are the most powerful enzymes that degrade aggrecan, a crucial constituent of the cartilage ECM (55-57). Meanwhile, cathepsins K, B, L, and S from the cysteine protease family are deemed the most significant enzymes in the progression of OA (58,59).

In healthy cartilage, it is necessary to achieve a balance between anabolic and catabolic processes to preserve homeostasis (51). However, if catabolic processes outweigh the chondrocytes' potential for regeneration, articular cartilage will degenerate. Therefore, targeting these catabolic enzymes, such as MMPs, ADAMTS, and cysteine proteases, could be a potential therapeutic approach for OA.

Several studies have investigated the association between ECM-degrading catabolic enzymes and OA. In 2014, a study investigated the impact of TIMP1, a glycoprotein, on MMPs and revealed that TIMP1 has the capacity to inhibit all MMPs by establishing complexes with high-affinity at one to one ratio (60). This discovery could potentially pave the way for novel OA treatment approaches.

Natural inhibitors of cysteine proteinase and uPA, such as cystatin C and plasminogen activator inhibitor-1 (PAI-1), respectively, have been identified (61,62). To better understand the chondroprotective function of DHEA, researchers conducted a study to investigate how DHEA affected these linked enzyme systems in the development of OA. According to *in vivo* conducted study, by regulating the metabolic balance of certain enzymes such as ADAMTS/TIMP-3 (63), uPA/PAI-1 (35), MMP-3/TIMP-1 (53), and cysteine proteinases/cystatin C, DHEA protects the cartilage from damage and degradation.

ADAMTS5 Interactions in OA

ADAMTS5 is a group of ADAMTS enzymes containing thrombospondin motifs and metalloproteinases. The ADAMTS family has 19 members in humans (64,65), with members 4 and 5 in the aggrecanases subgroup, which are responsible for tissue morphogenesis and pathophysiological remodeling (66). In arthritis, proteoglycan degradation is facilitated by ADAMTS4 and 5, leading to cartilage aggrecan degradation. Knee injuries increase the risk of post-traumatic OA, and while the relationship of subchondral bone and bone marrow lesions with OA is known, the response of the synovium to joint damage is not fully understood. A study conducted to determine changes in the synovium within the first 14 days of knee injury found that transcripts encoding ADAMTS4 increased in the synovium (67). In addition, the expression

of aquaporin 1 (AQP 1), a channel, increased in OA chondrocytes, and the downregulation of AQP 1 was found to decrease the expression of ADAMTS4, which suppresses IL-1β-induced ADAMTS4 (68). Therefore, the reduction of AQP 1 expression in OA can suppress ADAMTS4. OA is characterized by degenerative loss of articular cartilage in synovial joints, with changes in bone and synovium. The main culprit in aggrecan cleavage, an ECM component, is ADAMTS5 (69). In rats with medial meniscal tear, the OA group had a significant increase in ADAMTS5 at 4, 6, and 8 weeks compared to healthy controls and the placebo group, leading Elsadek et al. (70) to conclude that ADAMTS5 could serve as a serological marker in OA.

ADAMTS5, also known as aggrecanase 2, is a risk factor for degenerative disorders due to its overexpression, which is the main cause of joint destruction and matrix loss in OA (71). IL-1β induces ADAMTS5 expression in human chondrocytes, while WW domain-containing protein 2 (Wwp2) overexpression down-regulates it. Thus, Wwp2 is thought to regulate ADAMTS5 expression in articular cartilage (72). A recent study conducted in 2021 showed that ADAMTS5 is highly regulated in cartilage with OA and that miR-9-3p overexpression suppresses ADAMTS5 expression, leading to inhibition of IL-1β-induced apoptosis and ECM destruction. The study also found that MIR22HG inhibition reduced ECM degradation through the miR-9-3p/ADAMTS axis (73). A research study on the genetic variation of ADAMTS5 revealed that the polymorphism of rs2830585 contributes to the risk of OA in the knee. The study found that individuals with the TT genotype had a 1.95-fold higher risk of developing OA compared to those with the CC genotype, and the presence of the rs28305885T allele increased the risk of OA by 39% compared to individuals with the C allele (74). However, it was observed that the *ADAMTS5 rs226794* gene polymorphism was not associated with knee OA, and the G allele was not confirmed to be a risk factor for OA (75). In a study by Canbek et al. (64), the relationship between *OA* and *ADAMTS5* gene polymorphisms in Turkey was examined. As a result of the study, no significant difference was found in allele frequencies between the groups for the ADAMTS5 rs226794 and rs2830585 genotypes (64).

Age-related DNA damage is a known factor in the development of OA, as it can lead to cellular aging in joint tissue (76). To investigate the role of interferon genes (STING) in the pathogenesis of OA, a study was conducted in human and mouse cartilage. The study found that STING expression increased in OA patients and overexpression of STING led to increased expression of ADAMTS5. However, the use of lenti-sh-STING to destroy STING reversed the IL-1β-stimulated expression of ADAMTS5. Therefore, the study concluded that STING induces ECM degradation, contributing to the progression of OA (77).

Betulinic acid was found to reduce OA-like changes in a collagenase-injected mouse model by inhibiting the production of pro-inflammatory cytokines and the production of ADAMTS4 and 5 (78).

The TIMP family consists of four members, TIMP1-4, which are proteins with protease inhibitory effects. While TIMP3 is bound to the ECM, the others exist in a soluble form in the ECM. Selective inhibition of members of the ADAMTS family is achieved by TIMPs (79). A study carried out in 2016 aimed to identify the primary endogenous inhibitor of ADAMTS5 and ADAMTS4. The results revealed that TIMP-3 is the most significant inhibitor of ADAMTS4 and ADAMTS5 (80).

In a study investigating the effects of DHEA on the expression of aggrecanases and endogenous inhibitors of aggrecanases in a rabbit model of OA, cartilage treated with DHEA was found to have higher expression of TIMP-3 and lower expression of ADAMTS4 and ADAMTS5 compared to the control group, as determined by real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis. The results suggest that intra-articular administration of DHEA can decrease the gene expression of aggrecanases and increase the expression of the endogenous inhibitor TIMP-3, leading to a reduction in aggrecanase activity. This suggests that DHEA may be a beneficial treatment for OA by affecting the balance between aggrecanases and TIMP-3 (63).

NGF Pathways in OA

Musculoskeletal conditions such as OA and back pain remain prevalent and cause substantial distress and societal costs, despite considerable therapeutic progress in recent decades (81). To meet the pressing medical need for effective pain relief in these conditions, there is a demand for novel approaches and targeted therapies (81). NGF inhibitors offer a promising alternative to traditional drugs, which often pose risks of adverse effects on organs such as the gastrointestinal tract, heart, or kidneys (81). Although OA can manifest in various functional impairments, pain remains the principal symptom, and thus, pain management represents a key aspect of clinical care for OA patients (82).

NGF, the first growth factor to be identified, was discovered by Rita Levi-Montalcini in 1952. Subsequent studies in

the 1950s with Stanley Cohen showed that this factor regulated the growth and development of the nervous system (83). NGF belongs to a family of neurotrophic factors that includes brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 (84). Neurotrophins signal through tyrosine receptor kinases (Trk), also known as tropomyosin receptor kinases, including TrkA, TrkB, and TrkC. Among the neurotrophins, TrkA shows significant NGF specificity and binds to NT-3 as well (85).

Initially, NGF was identified as a soluble signaling protein produced by tumor tissue that promoted the survival and proliferation of sensory neurons (84). However, in the 1990s, it was discovered that NGF also contributes to tissue damage, discomfort, and pain in adults (83). NGF is released by immune cells involved in the inflammatory response to peripheral damage. Besides immune cells, non-immune cells such as endothelial cells, pericytes, chondrocytes, and synoviocytes may also produce NGF (83,86,87). Previous research has suggested that NGF does not immediately cause pain but rather contributes to pain by inducing peripheral and potentially central nerve sprouting (88). In an original study published by Testa et al. (89) in 2019, researchers investigated the relationship between NGF and pain by creating transgenic mice with the human *661C>T NGF* gene mutation. The study found that the nociception of heterozygous NGFR100W/wt mice was impaired (89). Recent studies have demonstrated that targeted inhibition of NGF is highly effective in animal models of many acute and chronic pain conditions while being notably free of side effects (90). Interestingly, research suggests that inflammation-induced NGF expression is seen in OA (84).

The Role of DHEA, NGF, and ADAMTS5 in the Treatment of OA and Current Treatments

Currently, there is no cure for OA. However, there are several forms of treatment available that can be grouped into the categories of reducing modifiable risk factors, intra-articular therapy, physical modalities, alternative therapies, and surgical treatments. In the early stages of OA, the primary goal of treatment is to alleviate stiffness and pain. As the disease progresses, the focus of treatment shifts towards maintaining physical function and preventing further damage (15).

OA is typically managed with first-line treatments such as NSAIDs and acetaminophen. However, if these options fail or are not appropriate, stronger medications like weak opioids and narcotic analgesics may be considered. Steroid injections into the affected joint can also be used for the management of inflammatory flares, although their effectiveness is limited and temporary. Intra-articular administration of hyaluronic acid and other viscosupplements can provide longer-lasting treatment, but their short-term efficacy is questionable and results are inconsistent (91-94). Conservative treatment approaches for OA primarily aim to alleviate symptoms, while arthroplasty is usually recommended for individuals with moderate to severe OA. For young patients seeking to preserve their knee function, osteotomy around the knee may be considered as an alternative surgical procedure, as it focuses on "knee preservation" (28). The effectiveness of these interventions may vary based on the severity of the condition (95). The effectiveness of OA treatment can be limited due to various factors, such as an individual's response to medications like NSAIDs and acetaminophen. Although these drugs can offer pain relief, their prolonged use can lead to serious negative effects and must be used with caution under medical supervision (96). While corticosteroid therapy can significantly improve outcomes in the short term, its regular use may promote cartilage deterioration, joint damage, or tissue atrophy (96). Unlike traditional treatments, in a study conducted in Turkey, autologous conditioned serum (ACS) treatment was tried. For this purpose, they performed bilateral knee injections. The results showed that the use of ACS resulted in significant improvement in pain severity and knee community scoring (97).

Additionally, lifestyle changes like weight loss and exercise can slow disease progression and reduce symptoms, but may not fully alleviate advanced stage symptoms (98). Surgeries, such as joint replacement, can provide significant function improvement and relief of pain, but they are invasive and carry risks like aseptic loosening, stiffness, prosthesis failure, instability, infection, and misalignment (99). OA treatment often involves a gradual process of multiple approaches, and it may not completely eliminate symptoms or restore function.

NGF

Studies using various OA models have demonstrated that anti-NGF drugs can effectively reduce pain-related behaviors, however, preclinical testing of NGF antibodies and TrkA inhibitors in OA models have lagged behind clinical trials (100). Utilizing preclinical models is important in understanding the mechanisms behind the analgesic relief provided by inhibiting the NGF/TrkA pathway in OA, as well as identifying the reasons and risk factors for rapid progression of the disease, which is often observed in clinical trials (100). Despite the lack of human use approval, anti-

NGF monoclonal antibodies (mAbs) are being developed as potential therapies for pain management in various conditions (101). Tanezumab (Pfizer in collaboration with Eli Lilly), fulranumab (Amgen), and fasinumab (Regeneron Pharmaceuticals in partnership with Sanofi) are currently humanized mAbs that have been developed to target free NGF as treatments (101). Clinical trials using NGF inhibition have been conducted in patients with hip and knee OA, which have shown that anti-NGF antibodies significantly reduce pain and improve function (102). A recent study by Ohashi et al. (26) 2021 aimed to investigate the relationship between pain, central sensitization, and synovial NGF expression in patients with hip OA who had undergone total hip replacements. The study found that in hip OA patients, synovial NGF expression is linked to both pain intensity and central sensitization, which supports the association between NGF molecule and pain (26). These findings demonstrate the potential for NGF inhibition as a promising therapeutic approach for OA pain management. In a 2019 study by Dakin et al. (103), 342 patients were given fasinumab, an anti-NGF monoclonal antibody drug, over a 36-week period to assess its efficacy and safety in OA. Results showed that fasinumab produced statistically significant and clinically meaningful pain reductions in comparison to placebo at all four dosages from baseline to week 16 (103).

The phase 3 study by Berenbaum et al. (104) in 2020 demonstrated significant pain relief, physical function improvement, and positive physician global assessment scores in patients with moderate-to-severe OA who had not responded to or could not tolerate standard-of-care analgesics after receiving subcutaneous tanezumab at a dose of 5 mg every 8 weeks. It is noteworthy that tanezumab is the most extensively researched anti-NGF drug and the most advanced agent, making it the likeliest candidate for regulatory approval among the anti-NGF drugs studied in OA (105). In 2019, Krupka et al. (106) published an original article evaluating the effectiveness and safety of GZ389988A, TrkA inhibitor, in participants with painful knee OA. Several pre-clinical OA models have demonstrated reduced pain behavior with TrkA inhibition, as TrkA is one of the receptors for NGF. This approach focuses on antagonizing both TrkA and p75NTR, the two NGF receptors, to decrease NGF-induced pain (105).

In a study by Krupka et al. (106) in 2019, 104 participants with moderate to severe knee OA pain were administered a single intra-articular injection of either GZ389988A, a TrkA inhibitor, or a placebo. The authors found that the injection of the TrkA inhibitor resulted in a sustained reduction in pain and a quantifiable functional improvement compared to the placebo. Additionally, the TrkA inhibitor demonstrated an acceptable safety profile (106). In 2020, Ishiguro et al. (107) conducted a study to evaluate the efficacy, safety, and tolerability of ONO-4474, a Pan-Tropomyosin Receptor Kinase inhibitor, in Japanese patients with knee OA. The study demonstrated that the drug effectively reduced pain in individuals with knee OA, supporting the association between blocking Trk and pain reduction in patients with OA, and further supporting the relationship between NGF molecule and pain (107). In contrast, a 2019 study by another research team investigated the efficacy of ASP7962, another TrkA inhibitor, in treating pain in knee OA. Despite a suitable study design, the oral small-molecule TrkA inhibitor did not improve pain in individuals with knee OA, and the authors confirmed the reliability of their results because of the significant improvement in pain observed between naproxen and placebo in the same study (108). According to the authors of the study, the discrepancy in results between their findings and other studies showing pain reduction after TrkA inhibitor administration may be due to the possibility that a higher dose of ASP7962 could have a stronger pharmacological effect, but this would need to be balanced against an increased risk of toxicity (108). Furthermore, the authors suggest that the slightly higher baseline pain levels in the ASP7962 group compared to the placebo group may have hindered the drug's ability to achieve a statistically significant effect (108). While the effectiveness of DHEA in reducing OA-related discomfort has not yet been confirmed, recent research suggests a potential relationship between DHEA's pharmacological actions and pain generation in OA (Figure 1). Given the lack of effective pharmaceutical options for treating OA, understanding the molecular pathways underlying DHEA's pain-relieving effects may pave the way for the development of novel anti-OA medications (25).

DHEA

In 2004, a study was conducted on a rabbit model to investigate the effects of DHEA treatment. Based on gross morphological examination and histological analysis, the results indicated that the femoral condyles that received DHEA treatment exhibited lower levels of cartilage damage compared to the untreated condyles (52). Additional evaluation to the overall structure of the cartilage, Safranin O staining, and thickness showed reduced damage in the DHEA group in comparison to the placebo group. The findings were further corroborated by the RT-PCR

based analysis of gene expression. These analysis has demonstrated a reduction in MMP-1/3 mRNA and IL-1 expression. Furthermore, TIMP-1 mRNA levels increase has also been detected in a treated knee joint cartilage with DHEA. These results indicate that DHEA may impede the catabolic degradation of MMPs in the OA process *in vivo* (109).

In 2015, a study using a rabbit model of OA examined the modifying effects of DHEA on the structure. The results demonstrated that DHEA treatment was capable of halting the advancement of pre-existing cartilage degeneration in various areas of the knee joint at different stages of OA, with certain variations possibly linked to the severity of the disease (38). In particular, in moderate OA, DHEA administration was found to prevent deterioration in both compartments of the knee. However, in advanced OA, DHEA was found to be effective only in inhibiting the deterioration of the lateral knee compartment. This site-specific and time dependent efficacy suggests that DHEA's structure-modifying effects against OA may vary depending on the location and stage of the disease. The multitargeted protective features of DHEA are illustrated in Figure 2. These findings suggest that understanding the molecular pathways of DHEA's protective effects on OA may lead to the development of new anti-OA medications, as there are currently no effective pharmaceuticals for treating OA.

ADAMTS5

Current treatments for OA are mainly aimed at relieving symptoms, such as the use of intra-articular drugs like NSAIDs and hyaluronic acid. Surgical options are considered for patients with end-stage OA. Disease-modifying osteoarthritis drugs (DMOADs) have the potential to alter the course of the disease by preventing structural changes in the joint and improving symptoms. One promising DMOAD is the anti-ADAMTS5 Nanobody M6495, which belongs to the proteinase inhibitor family (110). In an *ex vivo* cartilage model, M6495 demonstrated high affinity for the ADAMTS5 target and did not bind to ADAMTS4. In addition, it was observed that M6495 was able to completely inhibit the enzymatic activity of its target in a concentration-dependent manner (111).

A study conducted on rats with OA, bone marrow mesenchymal stem cell-derived exosomes were found to significantly reduce the upregulation of the IL-1β derived ADAMTS5 proteolytic enzyme, which researchers hypothesized was due to exosomes protecting chondrocytes

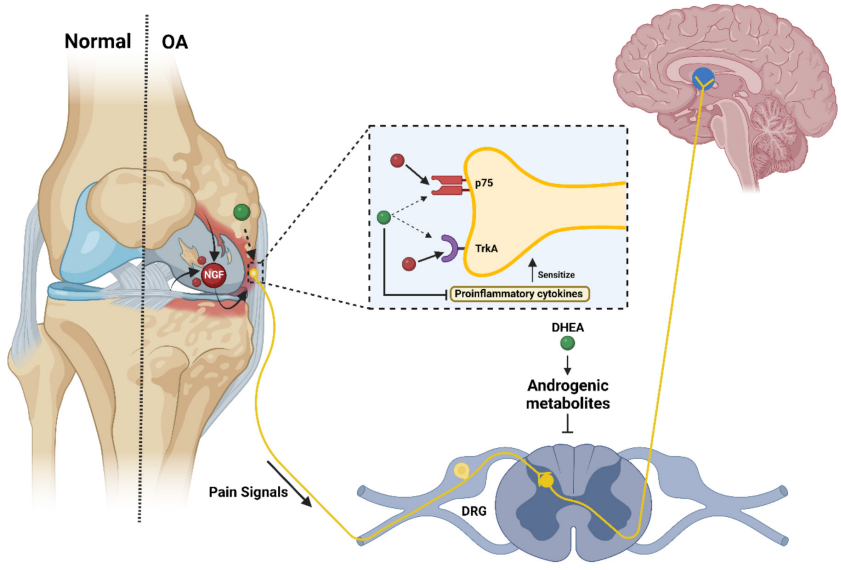

Figure 1. Interaction between DHEA and NGF-mediated pain pathwyas in osteoarthritis. This figure illustrates the intricate interaction between DHEA and NGF-mediated pain pathways in osteoarthritis. Nociceptor cells located in the peripheral regions of the body sense pain signals, which then travel to the dorsal horn of the spinal cord. The signal is then transmitted to the brain via the central terminals of the afferent nociceptors, which connect with second-order neurons in the dorsal horn. DHEA has the potential to reduce pro-inflammatory cytokines and block inhibitory mechanisms in the peripheral nervous system by suppressing NGF-mediated pain signaling, thereby preventing the transmission of pain signals from nociceptors in the joint capsule. Moreover, DHEA may be converted into androgen centrally, which can help to decrease the transmission of pain signals in the posterior horn of the spinal cord

DHEA: Dehydroepiandrosterone, NGF: Nerve growth factor, DRG: Dorsal root ganglion, OA: Osteoarthritis, TrkA: Tropomyosin-related kinase A

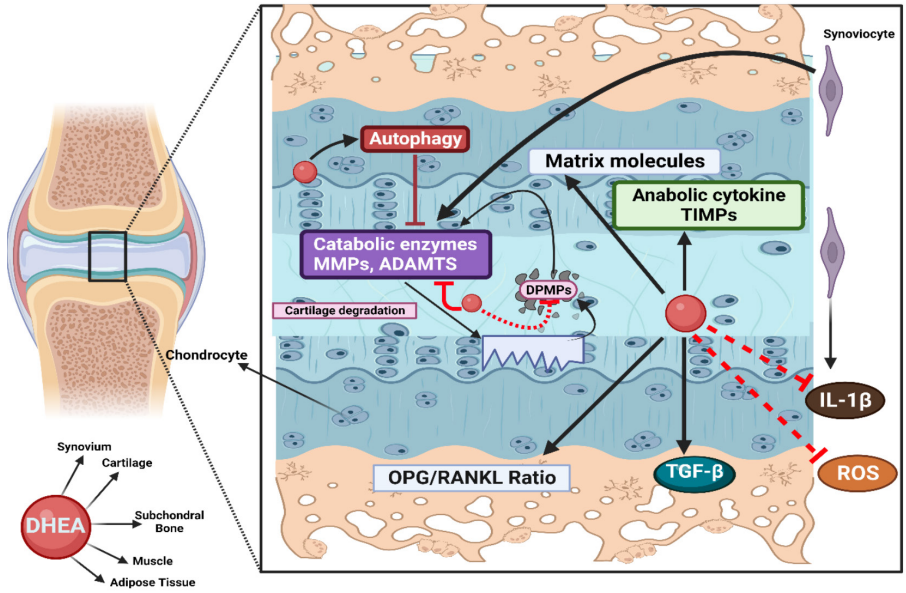

Figure 2. DHEA's multitargeted protective features are important for the various tissues affected by OA and the whole-joint pathology. This figure illustrates the multifaceted protective effects of DHEA on various tissues affected by OA and the overall joint pathology. DHEA influences the metabolic processes of different tissues involved in OA, including synovium, subchondral bone, cartilage, muscle, and fat. DHEA's potential mechanisms for preventing OA include: Reducing the release of damage-associated molecular patterns (DAMPs) and decreasing the production of catabolic enzymes, suppressing synovial inflammation by inhibiting IL-1β, enhancing chondrocyte autophagy, balancing the ratio of osteoprotegerin (OPG) and receptor activator of nuclear factor-kappa B ligand (RANKL) in subchondral bone, regulation of the signaling pathways of TGF-β in subchondral bone and cartilage, as well as the reduction of inflammation and oxidative stress in the near joint muscle

DHEA: Dehydroepiandrosterone, OA: Osteoarthritis

from IL-1β induced damage. The protective effect was also observed to be dose-dependent (112). Another potential therapeutic agent is hyperoside, a bioactive flavonoid with anti-inflammatory properties that has been shown to reduce ADAMTS5 expression and have anti-arthritic effects (113).

Aptamers are single-stranded DNA or RNAs with 3-dimensional structures that enable them to selectively bind to specific molecular targets (114). Recently, two new DNA aptamer inhibitors, apt 21 and apt 25, were developed, both of which demonstrated high binding affinity and specificity towards ADAMTS5. These aptamers exclusively inhibit ADAMTS5 activity and do not bind to ADAMTS4, making them potential candidates for the treatment of OA (115). A study conducted on rats with knee OA caused by monosodium iodoacetate (MIA) investigated the therapeutic potential of fibroblast growth factor-2 (FGF-2). The researchers overexpressed FGF-2 via rAAV-mediated gene transfer and found that inhibiting toll-like receptor 4 (TLR4) signaling and activating TIMP-1 downregulated ADAMTS5 mRNA and MMP13, markers of knee joint degradation. These results suggest that FGF-2 may have therapeutic benefits for MIA-induced knee OA (116).

In another study, Jia et al. (117) isolated and used murine primary chondrocytes to investigate the effect of cell-free fat extract (CEFFE) on ADAMTS5 expression. The researchers found that when primary chondrocytes were co-cultured with inflammation factors, ADAMTS5 expression increased, while treatment with CEFFE led to a reduction in ADAMTS5 expression. These findings suggest that CEFFE may be a promising therapeutic strategy for the treatment of OA (117).

In a study conducted in 2022, miR-17 was found to be expressed highly in the middle and superficial regions of articular cartilage and was observed to protect against the destruction of cartilage caused by destabilization of the medial meniscus by targeting pathological catabolic factors, including ADAMTS5. In the context of OA, miR-17 downregulation has been observed, which results in an increase in catabolic factors like ADAMTS5. The targeting of these genes by miR-17 suppresses the function of these catabolic factors and helps in maintaining cartilage homeostasis. Therefore, miR-17 could be a potential therapeutic target for the treatment of OA (118).

In a separate study conducted in 2022, researchers utilized IL-1β-treated chondrocytes as a cellular OA *in vitro* model

to assess the inhibitory impact of microRNA-613 (miR-613) on ADAMTS5. The researchers discovered the strong inhibitory effect of miR-613 on ADAMTS5 in this model, and the expression of ADAMTS5 was inversely correlated with the expression of miR-613. These results suggest that miR-613 may be a potential therapeutic target for OA by inhibiting ADAMTS5 expression in chondrocytes (119).

Conclusion

OA is a common condition that affects the joints and can cause pain and disability. Several molecules have been identified as being involved in the pathogenesis of OA, including:

- Pro-inflammatory cytokines such as TNF-α IL-1, which can promote the breakdown of cartilage and stimulate the formation of osteophytes (bone spurs).
- MMPs, enzymes that break down the ECM of cartilage.
- Reactive oxygen species, which can cause damage to cells and contribute to the development of OA.
- Aggrecanases, enzymes that break down the proteoglycan aggrecan, a major component of cartilage.
- Proteolytic enzymes such as ADAMTS4 and ADAMTS5 that can break down the ECM of cartilage.
- Cytokines (IL-1, IL-6, TNF-α) that are involved in promoting inflammation and pain in OA.

In treating OA, various methods such as therapy, medication, and in some cases, joint replacement surgery may be recommended to alleviate pain, improve joint function, and slow down the progression of the disease. Our review has predominantly focused on recent studies that aim to understand the role of DHEA, NGF, and ADAMTS5 in the pathophysiology of OA. These molecules play a significant role in distinct aspects of OA, such as cartilage breakdown, inflammation, and bone remodeling.

Currently, anti-NGF monoclonal antibodies are not a substitute for commonly used medications like NSAIDs. While ongoing research is exploring the effectiveness of targeting NGF as a treatment strategy for OA, there are no approved treatments that specifically target this molecule. On the other hand, targeting ADAMTS5 has shown promise as a treatment strategy for OA. Several ADAMTS5 inhibitors are currently under development, which specifically target the enzyme and inhibit its activity. As a result, these inhibitors slow down the destruction of cartilage. Additionally, it's worth noting that ADAMTS5 inhibitors are still in pre-clinical and clinical trial phases and not yet available on the market. Meanwhile, DHEA supplements have been suggested as a possible treatment for OA, but their effectiveness remains uncertain due to limited evidence, requiring more research to determine their efficacy in treating the condition. DHEA therapy is not commonly utilized for OA treatment as it lacks FDA approval for that indication, and further studies are necessary to evaluate its safety and effectiveness. The investigation of the molecular mechanisms underlying OA is still ongoing, and new molecules are continuously being discovered.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Drafting Manuscript: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Critical Revision of Manuscript: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Final Approval and Accountability: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K., Writing: D.S.A., N.H., O.A., E.B.Y., M.M.A-J., A.K.

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References

1. Hao HQ, Zhang JF, He QQ, Wang Z. Cartilage oligomeric matrix protein, C-terminal cross-linking telopeptide of type II collagen, and matrix metalloproteinase-3 as biomarkers for knee and hip osteoarthritis (OA) diagnosis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2019;27(5):726-736.
2. Nelson AE. Osteoarthritis year in review 2017: clinical. Osteoarthritis Cartilage 2018;26(3):319-325.
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014;73(7):1323-1330.
4. Hawker GA, King LK. The Burden of Osteoarthritis in Older Adults. Clin Geriatr Med 2022;38(2):181-192.
5. Liem Y, Judge A, Kirwan J, Ourradi K, Li Y, Sharif M. Multivariable logistic and linear regression models for identification of clinically useful biomarkers for osteoarthritis. Sci Rep 2020;10(1):11328.
6. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Ann Rheum Dis 2020;79(6):819-828.
7. Murphy LB, Cisternas MG, Pasta DJ, Helmick CG, Yelin EH. Medical Expenditures and Earnings Losses Among US Adults With Arthritis in 2013. Arthritis Care Res (Hoboken) 2018;70(6):869-876.

8. Jamshidi A, Pelletier JP, Martel-Pelletier J. Machine-learning-based patient-specific prediction models for knee osteoarthritis. Nat Rev Rheumatol 2019;15(1):49-60.

9. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. Curr Opin Rheumatol 2018;30(2):160-167.

10. Yan YS, Qu Z, Yu DQ, Wang W, Yan S, Huang HF. Sex Steroids and Osteoarthritis: A Mendelian Randomization Study. Front Endocrinol (Lausanne) 2021;12:683226.

11. Tschon M, Contartese D, Pagani S, Borsari V, Fini M. Gender and Sex Are Key Determinants in Osteoarthritis Not Only Confounding Variables. A Systematic Review of Clinical Data. J Clin Med 2021;10(14):3178.

12. O'Neill TW, McCabe PS, McBeth J. Update on the epidemiology, risk factors and disease outcomes of osteoarthritis. Best Pract Res Clin Rheumatol 2018;32(2):312-326.

13. Bilge A, Ulusoy RG, Üstebay S, Öztürk Ö. Osteoarthritis. Kafkas J Med Sci 2018;(1)133-142.

14. Martel-Pelletier J, Barr AJ, Cicuttini FM, Conaghan PG, Cooper C, Goldring MB, et al. Osteoarthritis. Nat Rev Dis Primers 2016;2:16072.

15. Abramoff B, Caldera FE. Osteoarthritis: Pathology, Diagnosis, and Treatment Options. Med Clin North Am 2020;104(2):293-311.

16. Weber AE, Bolia IK, Trasolini NA. Biological strategies for osteoarthritis: from early diagnosis to treatment. Int Orthop 2021;45(2):335-344.

17. Fuggle NR, Cooper C, Oreffo ROC, Price AJ, Kaux JF, Maheu E, et al. Alternative and complementary therapies in osteoarthritis and cartilage repair. Aging Clin Exp Res 2020;32(4):547-560.

18. Letizia Mauro G, Scaturro D, Gimigliano F, Paoletta M, Liguori S, Toro G, et al. Physical Agent Modalities in Early Osteoarthritis: A Scoping Review. Medicina (Kaunas) 2021;57(11):1165.

19. Özer D, Eyigör S. New therapy methods in osteoarthritis. Ege Journal of Medicine 2019;58: Supplement 14-21.

20. Morales-Ivorra I, Romera-Baures M, Roman-Viñas B, Serra-Majem L. Osteoarthritis and the Mediterranean Diet: A Systematic Review. Nutrients 2018;10(8):1030.

21. Molnar V, Matišić V, Kodvanj I, Bjelica R, Jeleč Ž, Hudetz D, et al. Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. Int J Mol Sci 2021;22(17):9208.

22. Kelwick R, Desanlis I, Wheeler GN, Edwards DR. The ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs) family. Genome Biol 2015;16(1):113.

23. Prough RA, Clark BJ, Klinge CM. Novel mechanisms for DHEA action. J Mol Endocrinol 2016;56(3):R139-R155.

24. Huang K, Wu LD. Dehydroepiandrosterone: Molecular mechanisms and therapeutic implications in osteoarthritis. J Steroid Biochem Mol Biol 2018;183:27-38.

25. Huang K, Cai HL, Wu LD. Potential of dehydroepiandrosterone in modulating osteoarthritis-related pain. Steroids 2019;150:108433.

26. Ohashi Y, Uchida K, Fukushima K, Satoh M, Koyama T, Tsuchiya M, et al. NGF Expression and Elevation in Hip Osteoarthritis Patients with Pain and Central Sensitization. Biomed Res Int 2021;2021:9212585.

27. Jiang Y, Tuan RS. Role of NGF-TrkA signaling in calcification of articular chondrocytes. FASEB J 2019;33(9):10231-10239.

28. Peng H, Ou A, Huang X, Wang C, Wang L, Yu T, et al. Osteotomy Around the Knee: The Surgical Treatment of Osteoarthritis. Orthop Surg 2021;13(5):1465-1473.

29. Ziogas A, Maekawa T, Wiessner JR, Le TT, Sprott D, Troullinaki M, et al. DHEA Inhibits Leukocyte Recruitment through Regulation of the Integrin Antagonist DEL-1. J Immunol 2020;204(5):1214-1224.

30. Lazaridis I, Charalampopoulos I, Alexaki VI, Avlonitis N, Pediaditakis I, Efstathopoulos P, et al. Neurosteroid dehydroepiandrosterone interacts with nerve growth factor (NGF) receptors, preventing neuronal apoptosis. PLoS Biol 2011;9(4):e1001051.

31. Schmelz M, Mantyh P, Malfait AM, Farrar J, Yaksh T, Tive L, et al. Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety. Pain 2019;160(10):2210-2220.

32. Gravanis A, Calogeropoulou T, Panoutsakopoulou V, Thermos K, Neophytou C, Charalampopoulos I. Neurosteroids and microneurotrophins signal through NGF receptors to induce prosurvival signaling in neuronal cells. Sci Signal 2012;5(246):pt8.

33. Veronese N, Maggi S, Noale M, Trevisan C, De Rui M, Bolzetta F, et al. Serum dehydroepiandrosterone sulfate and osteoarthritis in older people: the Pro.V.A. study. Clin Rheumatol 2016;35(10):2609-2614.

34. Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A, Rutkowski R. Dehydroepiandrosterone (DHEA): hypes and hopes. Drugs 2014;74(11):1195-1207.

35. Bao JP, Chen WP, Feng J, Zhao J, Shi ZL, Huang K, et al. Variation patterns of two degradation enzyme systems in articular cartilage in different stages of osteoarthritis: regulation by dehydroepiandrosterone. Clin Chim Acta 2009;408(1-2):1-7.

36. Li W, Tang L, Xiong Y, Zhou X, Wu L. The chondroprotective effects of dehydroepiandrosterone probably exerted by its conversion to estradiol. J Steroid Biochem Mol Biol 2013;134:15-22.

37. Jo H, Park JS, Kim EM, Jung MY, Lee SH, Seong SC, et al. The in vitro effects of dehydroepiandrosterone on human osteoarthritic chondrocytes. Osteoarthritis Cartilage 2003;11(8):585-594.

38. Huang K, Bao JP, Jennings GJ, Wu LD. The disease-modifying effect of dehydroepiandrosterone in different stages of experimentally induced osteoarthritis: a histomorphometric study. BMC Musculoskelet Disord 2015;16:178.

39. Bennett G, Cussen L, O'Reilly MW. The role for long-term use of dehydroepiandrosterone in adrenal insufficiency. Curr Opin Endocrinol Diabetes Obes 2022;29(3):284-293.

40. Hammer F, Subtil S, Lux P, Maser-Gluth C, Stewart PM, Allolio B, et al. No evidence for hepatic conversion of dehydroepiandrosterone (DHEA) sulfate to DHEA: in vivo and in vitro studies. J Clin Endocrinol Metab 2005;90(6):3600-3605.

41. Lang K, Burger-Stritt S, Hahner S. Is DHEA replacement beneficial in chronic adrenal failure? Best Pract Res Clin Endocrinol Metab 2015;29(1):25-32.

42. Rendina DN, Ryff CD, Coe CL. Precipitous Dehydroepiandrosterone Declines Reflect Decreased Physical Vitality and Function. J Gerontol A Biol Sci Med Sci 2017;72(6):747-753.

43. Calabrese V, Scapagnini G, Davinelli S, Koverech G, Koverech A, De Pasquale C, et al. Sex hormonal regulation and hormesis in aging and longevity: role of vitagenes. J Cell Commun Signal 2014;8(4):369-384.

44. Corrêa MS, Vedovelli K, Giacobbo BL, de Souza CE, Ferrari P, de Lima Argimon II, et al. Psychophysiological correlates of cognitive deficits in family caregivers of patients with Alzheimer Disease. Neuroscience 2015;286:371-382.

45. Sakr HF, Khalil KI, Hussein AM, Zaki MS, Eid RA, Alkhateeb M. Effect of dehydroepiandrosterone (DHEA) on memory and brain derived neurotrophic factor (BDNF) in a rat model of vascular dementia. J Physiol Pharmacol 2014;65(1):41-53.

46. Ohnaka K. Dehydroepiandrosterone (DHEA) and bone metabolism]. Clin Calcium 2016;26(7):987-993.

47. Savineau JP, Marthan R, Dumas de la Roque E. Role of DHEA in cardiovascular diseases. Biochem Pharmacol 2013;85(6):718-726.

48. Kirby DJ, Buchalter DB, Anil U, Leucht P. DHEA in bone: the role in osteoporosis and fracture healing. Arch Osteoporos 2020;15(1):84.

49. Sun JS, Wu CX, Tsuang YH, Chen LT, Sheu SY. The in vitro effects of dehydroepiandrosterone on chondrocyte metabolism. Osteoarthritis Cartilage 2006;14(3):238-249.

50. Li WJ, Tang LP, Xiong Y, Chen WP, Zhou XD, Ding QH, et al. A possible mechanism in DHEA-mediated protection against osteoarthritis. Steroids 2014;89:20-26.

51. Perini I, Elia I, Lo Nigro A, Ronzoni F, Berardi E, Grosemans H, et al. Myogenic induction of adult and pluripotent stem cells using recombinant proteins. Biochem Biophys Res Commun 2015;464(3):755-761.

52. Jo H, Ahn HJ, Kim EM, Kim HJ, Seong SC, Lee I, et al. Effects of dehydroepiandrosterone on articular cartilage during the development of osteoarthritis. Arthritis Rheum 2004;50(8):2531-2538.

53. Wu LD, Yu HC, Xiong Y, Feng J. Effect of dehydroepiandrosterone on cartilage and synovium of knee joints with osteoarthritis in rabbits. Rheumatol Int 2006;27(1):79-85.

54. Yeh CC, Chang SF, Huang TY, Chang HI, Kuo HC, Wu YC, et al. Shear stress modulates macrophage-induced urokinase plasminogen activator expression in human chondrocytes. Arthritis Res Ther 2013;15(2):R53.

55. Stanton H, Rogerson FM, East CJ, Golub SB, Lawlor KE, Meeker CT, et al. ADAMTS5 is the major aggrecanase in mouse cartilage in vivo and in vitro. Nature 2005;434(7033):648-652.

56. Verma P, Dalal K, Chopra M. Pharmacophore development and screening for discovery of potential inhibitors of ADAMTS-4 for osteoarthritis therapy. J Mol Model 2016;22(8):178.

57. Karsenty G. An aggrecanase and osteoarthritis. N Engl J Med 2005;353(5):522-523.

58. Mort JS, Beaudry F, Théroux K, Emmott AA, Richard H, Fisher WD, et al. Early cathepsin K degradation of type II collagen in vitro and in vivo in articular cartilage. Osteoarthritis Cartilage 2016;24(8):1461-1469.

59. Ben-Aderet L, Merquiol E, Fahham D, Kumar A, Reich E, Ben-Nun Y, et al. Detecting cathepsin activity in human osteoarthritis via activity-based probes. Arthritis Res Ther 2015;17(1):69.

60. Ries C. Cytokine functions of TIMP-1. Cell Mol Life Sci 2014;71(4):659-672.

61. Mathews PM, Levy E. Cystatin C in aging and in Alzheimer's disease. Ageing Res Rev 2016;32:38-50.

62. Mekkawy AH, Pourgholami MH, Morris DL. Involvement of urokinase-type plasminogen activator system in cancer: an overview. Med Res Rev 2014;34(5):918-956.

63. Huang K, Zhang C, Zhang XW, Bao JP, Wu LD. Effect of dehydroepiandrosterone on aggrecanase expression in articular cartilage in a rabbit model of osteoarthritis. Mol Biol Rep 2011;38(5):3569-3572.

64. Canbek U, Imerci A, Kara M, Akgun U, Canbek TD, Aydogan NH. Polymorphisms in ADAMTS4 and ADAMTS5 are not linked to susceptibility to knee osteoarthritis in the Turkish population. Genet Mol Res 2016;15(3).

65. Mohamedi Y, Fontanil T, Cal S, Cobo T, Obaya ÁJ. ADAMTS-12: Functions and Challenges for a Complex Metalloprotease. Front Mol Biosci 2021;8:686763.

66. Desanlis I, Felstead HL, Edwards DR, Wheeler GN. ADAMTS9, a member of the ADAMTS family, in Xenopus development. Gene Expr Patterns 2018;29:72-81.

67. Ayturk UM, Sieker JT, Haslauer CM, Proffen BL, Weissenberger MH, Warman ML, et al. Proteolysis and cartilage development are activated in the synovium after surgical induction of post traumatic osteoarthritis. PLoS One 2020;15(2):e0229449.

68. Haneda M, Hayashi S, Matsumoto T, Hashimoto S, Takayama K, Chinzei N, et al. Depletion of aquaporin 1 decreased ADAMTS4 expression in human chondrocytes. Mol Med Rep 2018;17(4):4874-4882.

69. Mead TJ, Apte SS. ADAMTS proteins in human disorders. Matrix Biol 2018;71-72:225-239.

70. Elsadek BEM, Abdelghany AA, Abd El-Aziz MA, Madkor HR, Abd Elrady Ahmed A, Abd-Elghaffar SK, et al. Validation of the Diagnostic and Prognostic Values of ADAMTS5 and FSTL1 in Osteoarthritis Rat Model. Cartilage 2021;13(Suppl 2):1263S-1273S.

71. Jiang L, Lin J, Zhao S, Wu J, Jin Y, Yu L, et al. ADAMTS5 in Osteoarthritis: Biological Functions, Regulatory Network, and Potential Targeting Therapies. Front Mol Biosci 2021;8:703110.

72. Mokuda S, Nakamichi R, Matsuzaki T, Ito Y, Sato T, Miyata K, et al. Wwp2 maintains cartilage homeostasis through regulation of Adamts5. Nat Commun 2019;10(1):2429.

73. Long H, Li Q, Xiao Z, Yang B. LncRNA MIR22HG promotes osteoarthritis progression via regulating miR-9-3p/ADAMTS5 pathway. Bioengineered 2021;12(1):3148-3158.

74. Zhou X, Jiang L, Zhang Y, Zhang J, Zhou D, Wu L, et al. Genetic variation of aggrecanase-2 (ADAMTS5) in susceptibility to osteoarthritis. Braz J Med Biol Res 2019;52(2):e8109.

75. Kao CC, Hsu HE, Chen YC, Tu MY, Chuang SW, Su SL. The Decisive Case-Control Study Elaborates the Null Association between ADAMTS5 rs226794 and Osteoarthritis in Asians: A Case-Control Study and Meta-Analysis. Genes (Basel) 2021;12(12):1916.

76. Coryell PR, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nat Rev Rheumatol 2021;17(1):47-57.

77. Guo Q, Chen X, Chen J, Zheng G, Xie C, Wu H, et al. STING promotes senescence, apoptosis, and extracellular matrix degradation in osteoarthritis via the NF-κB signaling pathway. Cell Death Dis 2021;12(1):13.

78. Han J, Guan J, Zhu X. β-Ecdysone attenuates cartilage damage in a mouse model of collagenase-induced osteoarthritis via mediating FOXO1/ADAMTS-4/5 signaling axis. Histol Histopathol 2021;36(7):785-794.

79. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF, et al. The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. Int J Mol Sci 2020;21(24):9739.

80. Li Y, Li K, Han X, Mao C, Zhang K, Zhao T, et al. The imbalance between TIMP3 and matrix-degrading enzymes plays an important role in intervertebral disc degeneration. Biochem Biophys Res Commun 2016;469(3):507-514.

81. Oo WM, Hunter DJ. Nerve Growth Factor (NGF) Inhibitors and Related Agents for Chronic Musculoskeletal Pain: A Comprehensive Review. BioDrugs 2022;35:611-641.

82. Conaghan PG, Cook AD, Hamilton JA, Tak PP. Therapeutic options for targeting inflammatory osteoarthritis pain. Nat Rev Rheumatol 2019;15(6):355-363.

83. Miller RE, Block JA, Malfait AM. Nerve growth factor blockade for the management of osteoarthritis pain: what can we learn from clinical trials and preclinical models? Curr Opin Rheumatol 2017;29(1):110-118.

84. Shang X, Wang Z, Tao H. Mechanism and therapeutic effectiveness of nerve growth factor in osteoarthritis pain. Ther Clin Risk Manag 2017;13:951-956.

85. Chao MV. Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci 2003;4(4):299-309.

86. Chartier SR, Mitchell SA, Majuta LA, Mantyh PW. Immunohistochemical localization of nerve growth factor, tropomyosin receptor kinase A, and p75 in the bone and articular cartilage of the mouse femur. Mol Pain 2017;13:1744806917745465.

87. Hiltunen JO, Laurikainen A, Väkevä A, Meri S, Saarma M. Nerve growth factor and brain-derived neurotrophic factor mRNAs are regulated in distinct cell populations of rat heart after ischaemia and reperfusion. J Pathol 2001;194(2):247-253.

88. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: the genesis of pain. Rheumatology (Oxford) 2018;57(Suppl 4):iv43-iv50.

89. Testa G, Mainardi M, Morelli C, Olimpico F, Pancrazi L, Petrella C, et al. The NGF^{R100W} Mutation Specifically Impairs Nociception without Affecting Cognitive Performance in a Mouse Model of Hereditary Sensory and Autonomic Neuropathy Type V. J Neurosci 2019;39(49):9702-9715.

90. Hefti FF, Rosenthal A, Walicke PA, Wyatt S, Vergara G, Shelton DL, et al. Novel class of pain drugs based on antagonism of NGF. Trends Pharmacol Sci 2006;27(2):85-91.

91. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006;2006(1):CD004257.

92. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16(2):137-162.

93. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ 2012;345:e4934.

94. Kodadek M. Managing osteoarthritis. Nurs Womens Health 2015;19(1):71-76.

95. Bhatia D, Bejarano T, Novo M. Current interventions in the management of knee osteoarthritis. J Pharm Bioallied Sci 2013;5(1):30-38.

96. Vaishya R, Pariyo GB, Agarwal AK, Vijay V. Non-operative management of osteoarthritis of the knee joint. J Clin Orthop Trauma 2016;7(3):170-176.

97. Kılınç BE, Öç Y. Evaluation of the autologous conditioned serum in the treatment of osteoarthritis. Archives Of Clinical And Experimental Medicine 2019;4(2):94-98.

98. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. Braz J Phys Ther 2021;25(2):135-146.

99. Roseti L, Desando G, Cavallo C, Petretta M, Grigolo B. Articular Cartilage Regeneration in Osteoarthritis. Cells 2019;8(11):1305.

100. Obeidat AM, Donner A, Miller RE. An update on targets for treating osteoarthritis pain: NGF and TRPV1. Curr Treatm Opt Rheumatol 2020;6(3):129-145.

101. Enomoto M, Mantyh PW, Murrell J, Innes JF, Lascelles BDX. Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats. Vet Rec 2019;184(1):23.

102. Wise BL, Seidel MF, Lane NE. The evolution of nerve growth factor inhibition in clinical medicine. Nat Rev Rheumatol 2021;17(1):34-46.

103. Dakin P, DiMartino SJ, Gao H, Maloney J, Kivitz AJ, Schnitzer TJ, et al. The Efficacy, Tolerability, and Joint Safety of Fasinumab in Osteoarthritis Pain: A Phase IIb/III Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Arthritis Rheumatol 2019;71(11):1824-1834.

104. Berenbaum F, Blanco FJ, Guermazi A, Miki K, Yamabe T, Viktrup L, et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase III study with a 24-week follow-up period. Ann Rheum Dis 2020;79(6):800-810.

105. Grässel S, Muschter D. Recent advances in the treatment of osteoarthritis. F1000Research 2020;9:1-17.

106. Krupka E, Jiang GL, Jan C. Efficacy and safety of intra-articular injection of tropomyosin receptor kinase A inhibitor in painful knee osteoarthritis: a randomized, double-blind and placebo-controlled study. Osteoarthritis Cartilage 2019;27(11):1599-1607.

107. Ishiguro N, Oyama S, Higashi R, Yanagida K. Efficacy, Safety, and Tolerability of ONO-4474, an Orally Available Pan-Tropomyosin Receptor Kinase Inhibitor, in Japanese Patients With Moderate to Severe Osteoarthritis of the Knee: A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Comparative Study. J Clin Pharmacol 2020;60(1):28-36.

108. Watt FE, Blauwet MB, Fakhoury A, Jacobs H, Smulders R, Lane NE. Tropomyosin-related kinase A (TrkA) inhibition for the treatment of painful knee osteoarthritis: results from a randomized controlled phase 2a trial. Osteoarthritis Cartilage 2019;27(11):1590-1598.

109. Shim IK, Yook YJ, Lee SY, Lee SH, Park KD, Lee MC, et al. Healing of articular cartilage defects treated with a novel drug-releasing rod-type implant after microfracture surgery. J Control Release 2008;129(3):187-191.

110. Oo WM, Little C, Duong V, Hunter DJ. The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date. Drug Des Devel Ther 2021;15:2921-2945.

111. Siebuhr AS, Werkmann D, Bay-Jensen AC, Thudium CS, Karsdal MA, Serruys B, et al. The Anti-ADAMTS-5 Nanobody® M6495 Protects Cartilage Degradation Ex Vivo. Int J Mol Sci 2020;21(17):5992.

112. He L, He T, Xing J, Zhou Q, Fan L, Liu C, et al. Bone marrow mesenchymal stem cell-derived exosomes protect cartilage damage and relieve knee osteoarthritis pain in a rat model of osteoarthritis. Stem Cell Res Ther 2020;11(1):276.

113. Sun K, Luo J, Jing X, Xiang W, Guo J, Yao X, et al. Hyperoside ameliorates the progression of osteoarthritis: An in vitro and in vivo study. Phytomedicine 2021;80:153387.

114. Zhu G, Chen X. Aptamer-based targeted therapy. Adv Drug Deliv Rev 2018;134:65-78.

115. Yu Y, Liu M, Choi VNT, Cheung YW, Tanner JA. Selection and characterization of DNA aptamers inhibiting a druggable target of osteoarthritis, ADAMTS-5. Biochimie 2022;201:168-176.

116. Rabie MA, Sayed RH, Venkatesan JK, Madry H, Cucchiarini M, El Sayed NS. Intra-articular injection of rAAV-hFGF-2 ameliorates monosodium iodoacetate-induced osteoarthritis in rats via inhibiting TLR-4 signaling and activating TIMP-1. Toxicol Appl Pharmacol 2023;459:116361.

117. Jia Z, Kang B, Cai Y, Chen C, Yu Z, Li W, et al. Cell-free fat extract attenuates osteoarthritis via chondrocytes regeneration and macrophages immunomodulation. Stem Cell Res Ther 2022;13(1):133.

118. Zhang Y, Li S, Jin P, Shang T, Sun R, Lu L, et al. Dual functions of microRNA-17 in maintaining cartilage homeostasis and protection against osteoarthritis. Nat Commun 2022;13(1):2447.

119. Yu Z, Cong F, Zhang W, Song T, Zhang S, Jiang R. Circular RNA circ_0020014 contributes to osteoarthritis progression via miR-613/ADAMTS5 axis. Bosn J Basic Med Sci 2022;22(5):716-727.