**Exploring Novel Non-Operative Treatments for Osteoarthritis: An Examination of Innovative Therapies**

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**Abstract:**

Osteoarthritis (OA) is a prevalent degenerative joint disease that significantly impacts the quality of life of millions worldwide, particularly the elderly. While conventional non-surgical treatments, such as NSAIDs, intra-articular injections, and physical therapy, provide symptomatic relief, their long-term efficacy and safety remain limited. Recent advancements in understanding OA pathophysiology have spurred the development of innovative therapeutic strategies targeting disease progression. This review examines emerging pharmacological and regenerative approaches, including disease-modifying osteoarthritis drugs (DMOADs), biologics, and cell-based therapies. Cutting-edge technologies such as RNA interference, CRISPR/Cas9, and advanced regenerative medicine are also explored for their potential to revolutionize OA management. Additionally, the integration of novel therapies with traditional interventions is discussed, highlighting opportunities for a more personalized, multimodal approach to OA care. Despite significant progress, challenges such as translational hurdles, cost barriers, and long-term efficacy require further investigation. This review emphasizes the transformative potential of emerging therapies in addressing the unmet needs of OA patients and shaping future treatment paradigms.

**Keywoards:** Osteoarthritis, emerging therapies, disease-modyfing osteoarthritis drugs, regenerative medicine, cell-based therapies, pain management, cartilage regeneration

**I. Introduction:**

OA is a chronic degenerative joint condition that affects millions of people worldwide, causing pain, loss of function, and disability, particularly in the elderly [1, 2]. As the leading cause of joint-related discomfort, OA poses a significant public health challenge, with the knee being the most impactful joint affected. Current treatment options for OA include non-pharmacological, pharmacological, and surgical interventions, but there is still no definitive cure [1, 3].

While traditional OA medications such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids have been widely used, they often provide limited relief and may have significant side effects [1, 2]. This has led to an increased focus on developing novel therapies, including DMOADs that aim to address the underlying causes of OA rather than just managing symptoms [1, 3]. Recent advancements in understanding OA pathophysiology have identified potential therapeutic targets against cartilage degeneration, subchondral bone remodeling, and synovial inflammation [3, 4].

Emerging therapies for OA include promising approaches such as biologics, cell-based regenerative therapies, and targeted molecular interventions [5, 6]. Additionally, innovative technologies like RNA interference (RNAi), CRISPR/Cas9, and PROTAC are being explored for their potential in treating OA [3, 6]. These advancements offer hope for more effective, personalized treatments that may not only alleviate symptoms but also potentially modify disease progression in the future [7, 8].

**II. Methods:**

This review of literature adopted a systematic and comprehensive approach to investigate progress in conservative treatments and novel therapies for OA. We employed a method to consolidate current research on OA and its emerging treatment options. An extensive search of literature was performed using databases including PubMed, Scopus, and Web of Science to identify pertinent studies published from 1997 to 2025. The review incorporated studies involving human subjects diagnosed with OA. Research was selected if it explored innovative and emerging therapies for OA and was published in peer-reviewed journals. Information from the chosen studies was collected using a uniform data extraction template to ensure consistency and precision. The gathered data underwent analysis to identify recurring themes, trends, and significant discoveries related to novel OA therapies. As this study is a review of previously published research, ethical approval was not required.

Informed consent was not applicable to this study as it did not involve direct interaction with human participants.

**III. Current Non-Surgical Treatment Landscape:**

**a. Pharmacological approaches: NSAIDs, acetaminophen, opioids**

Pharmacological approaches for OA primarily focus on pain management and inflammation reduction. NSAIDs, acetaminophen, and opioids are commonly used treatments, each with varying efficacy and safety profiles [9, 10]. NSAIDs have been a first-line treatment for decades, offering both analgesic and anti-inflammatory effects, but their long-term use is associated with gastrointestinal and cardiovascular risks [11, 12]. Acetaminophen, while often recommended as a first-choice agent due to its perceived safety, has shown poor analgesic properties in OA and may have underestimated gastrointestinal and cardiovascular toxicity [13]. Opioids, once considered effective for acute pain, have come under scrutiny due to the opioid crisis and their limited efficacy in chronic non-cancer pain conditions like OA [14].

**b. Non-pharmacological modalities: exercise, physical therapy**

Exercise and physical therapy play crucial roles in managing OA, particularly for knee and hip joints. Various studies have demonstrated the effectiveness of different exercise modalities in reducing pain, improving physical function, and enhancing quality of life for OA patients [15–17]. Aerobic training, strength training, and combination programs have shown significant benefits in pain reduction and functional improvement [18].

These interventions not only target OA symptoms but also help manage comorbidities and promote overall health

**c. Dietary supplements and nutraceuticals**

Nutraceuticals and dietary supplements have gained significant attention in the management of OA due to their potential to affect joint structure and alleviate symptoms [19]. These compounds play a role in balancing anabolic and catabolic signals in joints, making them increasingly considered for OA prevention and management [20]. Common nutraceuticals studied for OA include glucosamine, chondroitin sulfate, vitamins C and E, avocado-soybean unsaponifiables, omega-3 fatty acids, and botanical extracts [19–21].

**d. Intra-articular injections: Hyaluronic acid, corticosteroids**

Intra-articular injections of hyaluronic acid (HA) and corticosteroids are widely used treatments for OA, particularly in the knee and hip joints. Studies have shown that both HA and corticosteroids can provide pain relief and improve function in OA patients, though the effects may be modest and short-term [22, 23]. Corticosteroids tend to offer more immediate pain relief, while HA may provide longer-lasting benefits for functional capacity[23, 24]. However, the efficacy of these treatments can vary depending on the joint affected and the specific formulation used. Interestingly, recent evidence suggests that repeated corticosteroid injections might be associated with increased cartilage loss compared to saline injections, raising concerns about their long-term safety [25].

**IV. Emerging Pharmacological Therapies:**

**a. Serotonin-norepinephrine reuptake inhibitors**

Serotonin-norepinephrine reuptake inhibitors (SNRIs) have emerged as a promising pharmacological therapy for OA management. These drugs, which inhibit the reuptake of serotonin and norepinephrine, have shown effectiveness in pain relief for OA patients [2, 26]. SNRIs are considered among the novel treatments that offer potential alternatives to traditional OA drugs, which are often associated with adverse events and limited in their ability to reverse joint damage [26]. While SNRIs are primarily known for their use in treating depression and anxiety, their application in OA treatment highlights their versatility in addressing chronic pain conditions [27, 28]. This dual action on both serotonin and norepinephrine pathways may contribute to their efficacy in managing OA-related pain.

**b. IL-1 antagonists**

IL-1 antagonists have emerged as promising therapeutic agents for OA treatment. Interleukin-1 (IL-1), a key inflammatory and catabolic cytokine in OA pathophysiology, represents a potential target for disease modification [29]. Various strategies for inhibiting IL-1 production or activity have been investigated, including IL-1 receptor antagonist proteins, soluble IL-1 receptors, monoclonal antibodies against IL-1, and gene therapy approaches [29]. While IL-1 antagonists show promise, their clinical efficacy in human OA patients remains to be fully established. Further research and large-scale randomized controlled trials are needed to determine the long-term safety and efficacy of these emerging therapies [26, 30]. As OA is a complex, multifactorial disease, combination therapies targeting multiple pathways, such as IL-1Ra with lubricin (PRG4), may offer superior outcomes compared to monotherapies

**c. Antibodies to nerve growth factor**

Antibodies to nerve growth factor (NGF) have emerged as a promising therapeutic approach for OA pain management. Clinical trials have demonstrated the efficacy of anti-NGF therapies, such as tanezumab, in improving pain and function in OA patients [31, 32]. These antibodies work by blocking NGF, which plays a critical role in nociception and pain signaling [33]. The novel mechanism of action of NGF inhibitors differs from conventional drugs, offering a potential alternative for patients who do not respond well to traditional treatments like NSAIDs or opioids [32, 33]. However, the development of anti-NGF therapies has not been without challenges. Clinical trials revealed serious adverse effects, including rapidly progressive osteoarthritis and osteonecrosis, leading to a temporary moratorium on trials [31].

**d. Extended-release triamcinolone**

Extended-release triamcinolone acetonide (TA-ER) has emerged as a promising therapy for OA pain management. Formulated in poly(lactic-co-glycolic acid) (PLGA) microspheres, TA-ER allows for prolonged presence in the joint, reducing systemic exposure and associated adverse reactions [34]. In clinical trials, TA-ER demonstrated significant improvements in pain intensity, stiffness, and physical function compared to placebo and traditional triamcinolone acetonide crystalline suspension [34, 35]. The extended-release formulation provides 5-6 months of pain relief, potentially reducing the need for frequent injections [35].

**e. DMOADs**

DMOADs are emerging as promising therapies for OA, aiming to address the unmet need of disease modification rather than just symptom relief [1]. These novel drugs target various mechanisms involved in OA pathogenesis, including inflammation reduction, cartilage repair enhancement, and pain management [30, 36]. Potential DMOADs in development focus on inflammatory cytokines, matrix-degrading enzymes, the Wnt pathway, and OA-associated pain. Additionally, regenerative approaches aim to stimulate chondrogenesis and matrix anabolism [36].

Interestingly, while traditional OA treatments have shown limited success, recent advances in molecular understanding have reshaped the knowledge landscape. For instance, inflammation in OA appears distinct from that in rheumatoid arthritis, and genome-wide studies point to defects in repair pathways. This has led to promising results with growth factor therapies and Wnt pathway antagonism [37]. However, it's important to note that many of these new drugs are still in preclinical stages, and long-term randomized controlled trials are needed to establish their safety and efficacy[1, 30].

**V. Novel Biological Approaches**:

**a. Regenerative medicine techniques**

Regenerative medicine offers promising approaches for treating OA by addressing key challenges in stem cell-based therapies. Recent advancements have focused on enhancing the mechanical properties of tissue-engineered cartilage and improving integration of newly formed tissue within the joint. Novel strategies include direct injection of stem cells into the joint, manipulation of endogenous stem cells to enhance regenerative capacity, and utilizing stem cells for drug discovery [38]. Adipose-derived stromal cells (ASCs) have emerged as an attractive option for OA treatment due to their regenerative potential and ability to avoid in vitro expansion complications [39]. While significant progress has been made in understanding stem cell therapy challenges, current tissue engineering and regenerative medicine strategies still struggle to address the inflammatory environment in OA, which hinders cartilage regeneration. This highlights the need for incorporating immunomodulatory capabilities into engineered structures, such as optimizing biomaterial composition and loading anti-inflammatory molecules [40].

**b. RNA interference (RNAi) and CRISPR/Cas9 technologies**

RNA interference (RNAi) and CRISPR/Cas9 technologies have emerged as powerful tools for gene manipulation and functional genomics, with potential applications in OA research and treatment. RNAi, which uses small RNA molecules to silence specific genes, has been widely used for over a decade to study gene function and identify potential drug targets. On the other hand, CRISPR/Cas9, a more recent genome-editing technology, allows for precise insertions and deletions in the eukaryotic genome, offering new possibilities for understanding and potentially treating OA at the genetic level [41, 42]. Despite CRISPR/Cas9's growing popularity for its capacity to create inheritable genetic changes, RNA interference (RNAi) continues to offer distinct benefits in particular research context. For instance, RNAi can be more suitable for studying genes where complete knockout might be lethal or for targeting multiple genes simultaneously[42, 43]. In the context of OA, both technologies could be used to investigate the role of specific genes in disease progression or to develop novel therapeutic approaches.

**VI. Sports-Specific Considerations:**

**a. Prevention strategies for athletes**

Sport-specific considerations for preventing OA in athletes primarily focus on reducing the risk of joint injuries, particularly in high-impact sports. Early prevention strategies are crucial, as youth sports injuries, especially acute injuries to the knee and ankle, are likely linked to the development of OA later in life. For athletes participating in high-impact, high-stress elite sports at a young age, there may be an association with early OA development, though more long-term follow-up studies are needed to confirm this relationship [44]. Interestingly, the effectiveness of sports-specific injury prevention programs compared to general programs remains uncertain. A systematic review found that both general and mixed prevention strategies positively affected injury rates, but truly sports-specific programs were underinvestigated [45]. This highlights the need for more research into sport-specific prevention strategies for OA.

**b. Early intervention in sports-related injuries**

Early intervention in sports-related injuries is crucial for preventing the development of OA particularly in young athletes. Sports activities, while generally beneficial for health, can increase the risk of OA, especially in high-impact sports and at elite levels of participation [46]. Acute injuries to the knee and ankle, common in athletes, are strongly associated with the development of post-traumatic osteoarthritis (PTOA) [44, 47]. PTOA is particularly concerning due to its earlier onset and rapid progression compared to traditional OA, affecting younger and more active populations[47, 48]. Notably, the scientific literature presents conflicting findings regarding how various sports affect the risk of developing OA. While high-impact sports like soccer, rugby, and racket sports are associated with increased OA risk, low-impact activities such as walking, swimming, and cycling may have a protective effect [46, 49]. However, the long-term effects of continuing or ceasing sports practice on early OA progression remain unclear [49]. To prevent or delay the onset of OA, early intervention strategies should focus on proper rehabilitation, muscle strengthening, and neuromuscular control [48]. Addressing joint morphology, managing adiposity, and promoting physical activity are also crucial [48]. Additionally, early restoration of meniscal, ligament, and cartilage integrity is essential for protecting the joint and allowing safe return to sports[49]. Implementing injury prevention programs during childhood and adolescence may yield rewarding results in OA prevention [44, 50].

**c. Rehabilitation for athletes with OA**

Rehabilitation protocols for athletes with OA should incorporate a progressive, goal-oriented approach that combines medical management with therapeutic exercise. The program typically consists of five stages, starting with protected mobilization and pain control through medications and injections, then progressing to open and closed kinetic-chain exercises. Stage IV focuses on return to sporting activities, incorporating sport-specific exercises to improve neuromuscular coordination, timing, and injury prevention [51]. This stage is crucial for athletes, as it addresses the unique demands of their sport while managing their OA symptoms.

**d. Behavioral interventions for performance enhancement in athletes with OA**

Behavioral interventions have shown promise for enhancing performance in athletes with OA. While the reviewed papers do not specifically address OA, they provide insights into effective approaches that could be adapted for this population. Mindfulness-based interventions and psychological skills training have demonstrated positive effects on athletic performance[52, 53]. For athletes with OA, these interventions could be tailored to address pain management, body awareness, and adaptive coping strategies. Applied behavior analysis techniques have been used across various sports to improve performance[54] and could be modified to focus on movement patterns and pain-related behaviors in OA athletes.

**VII. Challenges and Future Directions:**

**a. Personalized medicine approaches for athletes**

Personalized medicine approaches for athletes with osteoarthritis face several challenges but also offer promising future directions. One major challenge is the need for standardized protocols and improved reliability across different imaging modalities used to assess cartilage damage and disease progression[55]. Additionally, the implementation of personalized approaches may be hindered by factors such as cost, test availability, patient adherence, and ethical considerations related to data harvesting from wearable devices[56, 57]. Despite these challenges, emerging technologies and strategies show great potential for advancing personalized medicine in this field. The integration of omics data, artificial intelligence, and big data analytics is enabling more precise pharmacogenomic selection of medications and the development of integrated risk-scoring systems[56]. Novel tissue engineering therapies and stem cell-based approaches are being explored to develop alternatives to total joint replacement, with recent studies showing progress in addressing key challenges such as the effects of age or disease on stem cell properties and improving scaffold designs [38].

**b. Integration of emerging therapies with traditional treatments**

The integration of emerging therapies with traditional treatments for OA presents both challenges and opportunities for future research and clinical practice. While conventional therapies primarily focus on symptom management, emerging treatments aim to modify disease progression and promote tissue regeneration[1, 38]. A key challenge lies in combining these approaches effectively, as traditional intra-articular therapies are not recommended as first-line treatments but may serve as alternatives when conventional methods fail [58]. The development of DMOADs represents a promising direction, targeting inflammation reduction and cartilage repair [1, 59]. However, many of these novel therapies are still in preclinical stages, necessitating long-term randomized controlled trials to establish their safety and efficacy [1]. The complexity of OA pathological mechanisms further complicates drug development and research [58].

**VIII. Conclusions:**

OA is a widespread and debilitating condition with limited curative options. Emerging therapies, including DMOADs, regenerative approaches such as stem cell therapies, and advanced technologies like CRISPR/Cas9, hold promise for addressing the underlying mechanisms of OA. These innovations aim not only to relieve symptoms but also to slow or modify disease progression.

However, many of these novel interventions remain in the experimental stages, with further large-scale clinical trials required to establish their safety and efficacy. Continued research and integration of these therapies into multimodal treatment strategies are essential to improving patient outcomes and advancing OA management.

**Disclosure**

**Author's contribution**

Conceptualization: J. Zygadło ; methodology: P. Bakuła; software: K. Jałocha; check: J. Zygadło; formal analysis: P. Bakuła; investigation: K. Jałocha; resources: J. Zygadło; data curation: P. Bakuła; writing-rough preparation: J. Zygadło; writing – review and editing: P. Bakuła; visualization: K. Jałocha; supervision: J. Zygadło; project administration: P. Bakuła

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The authors deny any conflict of interest.

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