New insights into physiotherapeutic treatment of osteoarthritis

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Abstract
Osteoarthritis (OA) is the most common chronic joint disease and the leading cause of disability in older adults. In this paper, we aimed to determine whether new findings about the pathophysiology of OA have an impact on the physiotherapeutic treatment of patients with OA. The disease has a complex pathophysiology, an important part of which, in addition to mechanical factors, are the presence of local and systemic low-grade inflammation and metabolic factors that cause structural changes in articular cartilage, subchondral bone, synovial membrane, ligaments and periarticular muscles. These influence the development of characteristic symptoms such as pain, stiffness, reduced mobility and crepitus. However, in the last decade, several studies have shown that, in addition to pathological changes of the articular structures in OA, neuroplastic changes of the CNS are also present and have a significant impact on the processing of osteoarthritic pain. Osteoarthritis is therefore not just a disease of the synovial joints, but a complex syndrome that affects the whole person. We concluded that these new insights and the complexity of the pathophysiology of OA allow for new methods of treatment beyond a purely biomechanical approach. Thus, in addition to traditional methods of treatment, it is reasonable to include new innovative methods such as pain neuroscience education, cognitive functional therapy, graded motor imagery, visuo-tactile illusions, virtual reality training, and behavioral graded activity to influence neuroplastic changes of the central nervous system and associated symptoms present in patients with OA. By incorporating various forms of exercise therapy, we can help reduce the presence of local and systemic inflammation, which are also important factors in the pathophysiology of OA. Key words: osteoarthritis, pathophysiology, physiotherapeutic treatment, new insights, neuroplastic changes

Nova spoznanja v fizioterapevtski obravnavi osteoartritisa

Povzetek
Osteoartritis (OA) je najpogostejša kronična bolezen sklepov in je vodilni vzrok invalidnosti pri starejših odraslih. Cilj študije je bil ugotoviti ali nova spoznanja s področja patofiziologije OA vplivajo na princip fizioterapevtske obravnave pacientov z OA. Bolezen ima kompleksno patofiziologijo, katere pomemben del poleg mehanskih dejavnikov predstavljajo tudi prisotnost lokalnega in sistemskega vnetja nizke stopnje ter presnovni dejavniki, ki povzročajo strukturne spremembe sklepnega hrustanca, subhondralne kosti, sinovialne membrane, ligamentov in periartikularnih mišic, ki vplivajo na nastanek značilnih simptomov, kot so bolečina, okorelost, zmanjšana gibljivost in krepitus. V zadnjem desetletju pa so številne študije pokazale, da so poleg patoloških sprememb sklepnih struktur pri OA prisotne tudi nevroplastične spremembe CŽS, ki pomembno vplivajo na procesiranje bolečine. Za osteoartritis bi tako lahko rekli, da ni le bolezen sinovialnih sklepov, temveč gre za zapleten sindrom. Ugotovili smo, da ta nova spoznanja in kompleksnost patofiziologije OA omogočajo nove oblike obravnav, ki presegajo zgolj biomehanski pristop. V obravnavo pacientov z OA je tako poleg klasičnih oblik smiselno vključiti tudi nove inovativne metode, kot so edukacija o nevroznanosti bolečine, kognitivna funkcionalna terapija, stopnjevana motorična predstava, vidno taktilne iluzije, vadba z virtualno resničnostjo in vedenjsko stopnjevana aktivnost, s katerimi lahko vplivamo na nevroplastične spremembe CŽS in z njimi povezane simptome, ki so prisotni pri pacientih z OA. Z vključevanjem različnih oblik vadbene terapije pa lahko pripomoremo k zmanjševanju prisotnosti lokalnega in sistemskega vnetja, ki sta tudi pomembna dejavnika v patofiziologiji OA. Ključne besede: osteoartritis, patofiziologija, fizioterapevtska obravnava, nova spoznanja, nevroplastične spremembe

INTRODUCTION

Osteoarthritis (OA) is the most common chronic disease of the synovial joints and causes structural changes to the entire joint. It is estimated that 528 million people worldwide are currently affected by OA and it is the leading cause of disability in older adults (O'Neill & Felson, 2018; Roos et al., 2022). Osteoarthritis most commonly affects the knee joint, followed by the hip joint and the small joints of the hands and fingers (Hunter & Bierma-Zeinstra, 2019). For a long time, the prevailing view was that OA is a passive degenerative disease that occurs as a result of wear and tear on the joint due to overuse and overloading. However, more recent studies suggest that OA has a complex pathophysiology involving mechanical as well as inflammatory and metabolic factors, which in turn lead to structural changes in the hyaline cartilage, subchondral bone, ligaments, joint capsule, synovium and periarticular muscles. Osteoarthritis is thus a disease in which active and dynamic changes resulting from an imbalance between injury and repair of joint structures occur and affect the entire joint (Hunter & Bierma-Zeinstra, 2019). The disease can be divided into primary OA, in which the cause of its occurrence is unknown, and secondary OA, which results from trauma, disease and obesity (Abramoff & Caldera, 2020). The most common risk factor for the development of OA is age, which is associated with increasing changes in joint structures. Other known risk factors for the development of OA are gender, obesity, previous joint injuries, dysplasia, sports activities (hockey), heavy occupations (construction) and genetics (Hunter & Bierma-Zeinstra, 2019). The main symptoms of OA are pain, joint stiffness and reduced joint function. Other common symptoms are reduced range of motion, joint instability, crepitus, swelling, muscle weakness and psychological problems, which are mainly related to the onset of pain. Of all the symptoms, pain is the most disabling and is usually the main reason why patients seek help. Pain is also the main driver of clinical decision-making. In fact, there are two types of pain in OA. The first is intermittent pain, which is present in the early stages of the disease, is predictable and is triggered by activity and stress on the joint, and constant pain, which occurs as the disease progresses and is also present at rest (Fu et al., 2018). The history, where patients report pain, short morning stiffness and functional limitations, and the clinical examination, which shows limited joint mobility, crepitus, joint tenderness and the presence of bony prominences, play a key role in the diagnosis. Imaging is not essential for the diagnosis, but can help to confirm it and exclude alternative diagnoses (Hunter & Bierma-Zeinstra, 2019). Osteoarthritis is a condition for which there is currently no cure that has been proven to slow the progression of the disease. The treatment of OA can be divided into the groups of non-pharmacological, pharmacological, non-surgical and surgical treatments. Current guidelines tend to focus on non-pharmacological and non-surgical treatments as the first choice in the management of OA (Holden et al., 2023). For the latter, physiotherapy plays an important role in helping to maintain and improve functional capacity and alleviate symptoms that occur in OA. The methods and techniques most commonly used in physiotherapy treatment of OA are kinesiotherapy, education and manual therapy. Studies have shown that kinesiotherapy, consisting of muscle strengthening exercises and exercises to improve general aerobic fitness, is one of the key elements in the management of knee and hip OA, as it helps to improve functional capacity and reduce pain. However, exercise also plays an important role in coping with obesity, which is one of the important risk factors for OA (Hunter & Bierma-Zeinstra, 2019; Kolasinski et al., 2020). However, the complexity of the pathophysiology of OA and new insights in this field suggest that further studies are needed on novel approaches in the management of OA beyond the primary biomechanical approach used so far. The aim of this article is to provide a review of the latest research findings on new insights into the pathophysiology of osteoarthritis and their impact on physiotherapeutic treatment.

METHODS

The literature was retrieved from PubMed electronic database and from review of the references of existing studies. A variety of combinations of the following keywords were used in the literature search: osteoarthritis, pathophysiology, physiotherapy, rehabilitation, inflammation, metabolism, pain and exercise. Inclusion criteria included studies on osteoarthritis, osteoarthritis pathophysiology and physiotherapeutic treatment of people with osteoarthritis, review articles, systematic literature reviews, randomized and controlled clinical trials, meta-analyses and studies written in English or Slovenian language. Exclusion criteria included studies published before 2005.

RESAULTS

A total of 1,368 studies were identified in the PubMed database. By applying further filters in accordance with the pre-established inclusion criteria and eliminating duplicates, the initial set of studies was reduced to 426. Subsequently, the remaining studies were subjected to a title and abstract screening, resulting in the exclusion of a further 312 studies that did not meet the eligibility criteria. This resulted in 114 studies being included in the detailed review and analysis. Of these, 97 were ultimately excluded due to their substantive inadequacy. Therefore, 17 studies from the PubMed database were ultimately included in the results. In addition to the PubMed database, three further studies were identified following a review of the references of existing studies. All three studies were included in the final analysis following a comprehensive review. The total number of studies included in the results of our literature review is thus 19. The process of study selection for the results of our literature review, which was conducted using the PRISMA diagram is shown in Figure 1. The selected studies were then divided into two groups, as presented in Tables 1 and 2. Table 1 presents studies related to the pathophysiology of OA, while Table 2 presents studies related to the physiotherapeutic treatment of patients with OA.

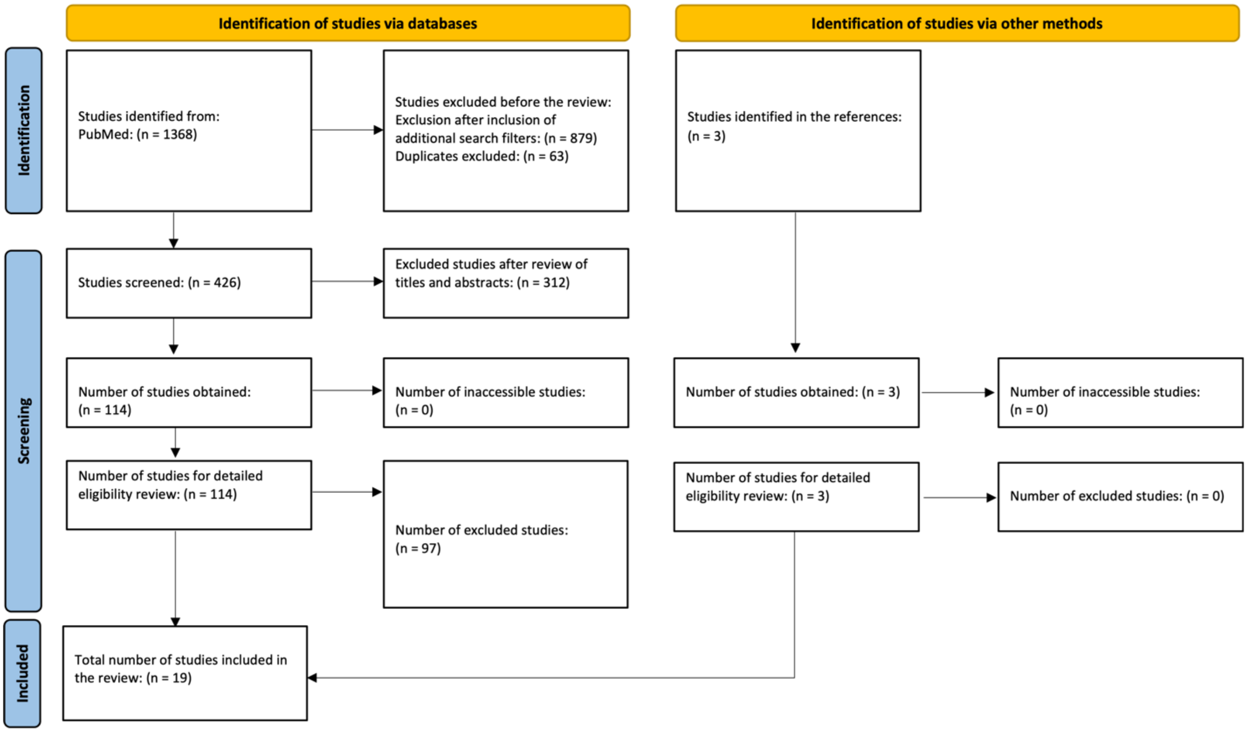

Figure 1: PRISMA Flow Diagram (Page et al., 2021)

Table 1: Pathophysiology of osteoarthritis

PUBLICATION	AIM/METHODS	CONCLUSIONS/RESULTS
Mechanical loading, cartilage degradation, and arthritis Sun, 2010	The aim of this review was to investigate the role of non-physiological mechanical loads on the joint in articular cartilage degradation and OA.	Both overloading and underloading of the joint cause degradation of the articular cartilage, which over time can lead to OA?
Molecular mechanisms of mechanical load-induced osteoarthritis Fang et al., 2021	The aim of this study was to review the literature ion the molecular mechanisms of excessive mechanical loading leading to OA.	Studies show that excessive mechanical stresses lead to the activation of different molecular pathways that cause *ECM degradation and chondrocyte apoptosis, leading to OA.

The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis Sellam and Berenbaum, 2010	The aim of this systematic review was to present the role of synovitis in the pathophysiology of OA and in the development of its characteristic symptoms.	Synovitis in one of the key factors in the pathophysiology of OA. Inflammation of the synovial membrane contributes to cartilage degradation through several catabolic and pro-inflammatory mediators.
Metabolic triggered inflammation in osteoarthritis Wang et al., 2015	The aim of this paper was to investigate the link between meta-inflammation and OA and how different components of meta-inflammation contribute to the development of OA.	Meta-inflammation plays an important role in the pathogenesis of OA. Chronic low-grade inflammation causes a range of inflammatory changes in OA.
Spatially defined disruption of motor imagery performance in people with osteoarthritis Stanton et al., 2021	The aim of this study was to determine whether motor performance is impaired in patients with knee OA and whether these impairments are related to the location of pain.	They discovered that implicit motor imagery is impaired in OA patients in a spatially defined manner.
Tactile acuity is disrupted in osteoarthritis but is unrelated to disruptions in motor imagery performance Stanton et al., 2013	The aim was to determine whether people with painful knee OA have impaired tactile acuity and whether this is related to their motor performance.	People with painful knee OA have reduced tactile acuity, which is a clinical sign of the presence of impaired knee performance in *S1.
Organisation of the motor cortex differs between people with and without knee osteoarthritis Shanahan et al., 2015	The aim of the study was to determine whether there are changes in the organization of the motor cortex in people with OA compared to healthy individuals, and to determine if these changes affect the accuracy of motor task performance.	People with knee OA have changes in the organization of the motor cortex. The study also found that people with knee OA have poorer motor task performance. This suggests the possibility of a mechanistic link between cortical changes and altered motor behavior in people with OA.
Evidence for distorted mental representation of the hand in osteoarthritis Gilpin et al., 2014	The aim of this study was to investigate whether people with painful hand OA have a distorted representation of the size of the affected limb and whether this representation is variable.	The study found that hand OA is associated with a distorted mental representation of the painful limb.
Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review Lluch et al., 2014	The aim of this systematic review was to determine whether there is evidence for a role of *CS in OA-related chronic pain and to summarize the current evidence on the role of *CS in OA.	Researchers have found that most OA patients experience *CNS hypersensitivity, and that *CS plays a key role in the pain-related problems reported by OA patients.
Sensitization in patients with painful knee osteoarthritis Arendt-Nielsen et al., 2010	The aim of this study was to investigate the role of sensitization in patients with knee OA.	The study found that central sensitization is one of the possible mechanisms of pain in OA.
Structural and functional brain changes in people with knee osteoarthritis: a scoping review Salazar-Mendez et al., 2023	The aim of the review was to examine the evidence of structural and functional changes in the brain that occur in patients with knee OA.	A review of the literature showed that patients with knee OA have neuroplastic changes in areas of the brain responsible for pain processing.

*S1 - primary somatosensory cortex; *CS - central sensitization; *CNS - central nervous system

Table 2: Physiotherapeutic treatment of patients with osteoarthritis

PUBLICATION	AIM/METHODS	CONCLUSIONS/RESULTS
Neurophysiological pain education for patients with symptomatic knee osteoarthritis: A systematic review and meta-analysis Lesmond et al., 2023	The aim of this review was to investigate the effectiveness of *PNE in the treatment of patients with. knee OA, considering pain-related variables.	*PNE, alone or in combination with other methods, was found to significantly help reduce the pain and pain-related catastrophizing in patients with knee OA.

Process of change for people with knee osteoarthritis undergoing cognitive functional therapy: a replicated single-case experimental design study Caneiro et al., 2023	The aim of this study was to examine the applicability of *CFT in the management of pain and disability in patients with knee OA.	The study demonstrated the applicability of *CFT in the management of people with knee OA. Two different responses were detected. The first showed a clear shift towards a biopsychosocial conceptualization of OA, the second a mixed conceptualization with incongruent beliefs about disease.
Does graded motor imagery benefit individuals with knee pain: A systematic review and meta-analysis Galonski et al., 2023	The aim was to determine whether individuals with knee pain have changes in CNS processing and function, and to examine the effects of *GMI on reducing pain and improving knee function.	Individuals with knee OA have deficit in CNS processing. However, the application of *GMI in the rehabilitation process of OA patients could be effective in reducing pain.
Illusory resizing of the painful knee is analgesic in symptomatic knee osteoarthritis Stanton et al., 2018	The aim of this study was to determine whether visuotactile illusions have analgesic effects in people with painful knee OA.	They discovered that illusory knee resizing with visuotactile manipulation has an analgesic effect in people with osteoarthritic pain but requires multisensory input to achieve these effects.
Efficacy of virtual reality exercise in knee osteoarthritis rehabilitation: a systematic review and meta-analysis Wei et al., 2024	The aim of this systematic review and meta-analysis was to investigate the effects of *VR exercise on pain, function and muscle strength in patients with knee OA.	*VR exercise significantly increases muscle strength and alleviates pain in patients with knee OA. However, the improvement in functional capacity is not that significant.
Effectiveness of Behavioral Graded Activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial Veenhof et al., 2006	The aim of this randomized clinical trial was to compare the effectiveness of *BGA with conventional forms of physiotherapeutic treatment in patients with hip and/or knee OA.	Both conventional physiotherapeutic treatment and *BGA have been found to have positive effects in the management of patients with knee and/or hop OA.
Behavioural graded activity results in better exercise adherence and more physical activity than usual care in people with osteoarthritis: A cluster-randomised trial Pisters et al., 2010	The aim of the study was to determine whether *BGA, compared to conventional treatments, increases OA patients' engagement in exercise therapy and whether it increases daily physical activity in individuals with OA.	The results of the study showed that *BGA increases daily physical activity in individuals with OA and improves their engagement in exercise therapy.
Exercises-induced effect on inflammatory markers and brain-derived neurotrophic factor in patients with knee osteoarthritis: a systematic review with meta-analysis Puts et al., 2023	The aim of this systematic review was to investigate the basal end acute effects of therapeutic exercise on biomarkers of inflammation and *BDNF in patients with knee OA.	Exercise therapy is effective in inducing an immunomodulatory response in patients with knee OA and has been shown to reduce local and systemic inflammation. Evidence for basal and acute effects of exercise training was also found.

*PNE - pain science education; *CFT - Cognitive functional therapy; *GMI - graded motor imagery; *VR - virtual reality; *BGA - behavioral graded activity; *BDNF - brain-derived neurotrophic factor

DISCUSSION

Osteoarthritis is the most common chronic progressive joint disease currently understood to result in structural and functional alterations, affecting not only the articular cartilage but also the joint as a whole (Goldring et al., 2017). The pathophysiology of OA is thus characterized by progressive deterioration and calcification of articular cartilage, inflammation of the synovial membrane, changes in subchondral bone structure and osteophyte formation (Goldring et al., 2017). However, the development of these pathological changes in joint structures is influenced by a number of factors, including mechanical factors. While mechanical loading of the joint is vital for maintaining joint homeostasis, non-physiological loads, such as overloading or underloading of the joint, can result in the degradation of articular cartilage and the development of OA (Sun, 2010). The role of non-physiological joint loading in the degradation of articular cartilage and the development of arthritis was investigated by Sun (2010). In his study, Sun (2010) states that damage to articular cartilage resulting in its degradation can be caused by both acute and chronic overloading of the joint. It has been demonstrated that prolonged mechanical overloading of the joint can directly damage the ECM of the cartilage and disrupt the balance of chondrocytes, thereby allowing catabolic processes to predominate over anabolic processes (Sun, 2010). Similar to mechanical overloading of the joint, Sun (2010) states that increased catabolic activity in the joint is the result of underloading of the joint, which can be caused by immobilization or various acute injuries. Insufficient loading of the joint results in thinning of the articular cartilage and a reduction in proteoglycan content, which in turn leads to ulceration and fibrillation of the cartilaginous extracellular matrix (Sun, 2010). Fang et al. (2021) found that excessive mechanical loading of the joint influences the development of OA through a number of molecular pathways. Specifically, when the joint is overloaded, the IL-1β, TNF-α, oxidative stress, nuclear factor kappa B (NF-κB), microRNA and Wnt signaling pathways are activated, which are involved in the regulation of inflammation in the joint and the activation of proteolytic enzymes, such as MMPs and ADAMTS, which play a pivotal role in the degradation of articular cartilage (Fang et al., 2021). In addition, they also cause chondrocyte apoptosis, cartilage matrix degradation, subchondral bone dysfunction and synovial membrane inflammation, leading to the pathogenesis of OA (Fang et al., 2021). In addition to mechanical factors, inflammation also plays an important role in the pathophysiology of OA. As described by Sellam and Berenbaum (2010) in their systematic review, one of the key factors in the pathophysiology of OA is inflammation of the synovial membrane, termed synovitis. In addition to structural alterations in the cartilage, OA patients also present with hypertrophy of the synovial membrane and increased vascularity, as well as infiltration of inflammatory cells into the synovial membrane (Sellam & Berenbaum, 2013). These alterations in the synovial membrane are evident in both the early and advanced stages of OA. Inflammation of the synovial membrane also influences the onset of some clinical symptoms, such as inflammation-related pain and joint swelling (Sellam and Berenbaum, 2010). This is due to the fact that the inflamed synovial membrane produces a number of proinflammatory and catabolic mediators such as cytokines, prostoglandin E2, neuropeptides and nitric oxide, which cause an imbalance between the degradation and repair of the cartilaginous extracellular matrix (Sellam and Berenbaum, 2010). The production of these mediators in turn leads to the overproduction of MMPs and ADAMTS, which cause the degradation of articular cartilage (Sellam and Berenbaum, 2010). In addition to local inflammation, there is also growing evidence to suggest that systemic inflammation plays a role in the pathogenesis of OA. Studies have shown that obesity not only influences the development of OA through increased body weight and body mass index, but also that body fat plays an even more important role (Wang et al., 2015). In fact, fat cells, which are the main building blocks of adipose tissue, synthesize a number of cytokines and adipokines that are involved in the development of inflammation (Wang et al., 2015). Adipose tissue thus functions as a metabolic endocrine organ, releasing adipokines such as leptin, visfatin, resistin and adiponectin, which result in metabolic dysfunction in OA patients (Wang et al., 2015). Adipokines are involved in regulating local inflammatory processes and causing structural degradation of the joints, thereby disrupting homeostasis in cartilage (Wang et al., 2015). Researchers have found that leptin is associated with an increased loss of articular cartilage thickness and a decrease in articular cartilage volume (Wang et al., 2015). In addition to adipokines, a number of pro-inflammatory cytokines are also present in adipose tissue, including IL-1β, IL-6 and TNF-α, which play a major role in the release of anabolic enzymes and inhibit the synthesis of type II collagen and proteoglycans, which are key components of the cartilage extracellular matrix (Wang et al., 2015). Abnormalities in body composition, adipokines, cytokines and other components thus lead to the formation of metabolically triggered inflammation (meta-inflammation), which, in addition to the synovitis described previously, causes many of the pro-inflammatory changes in OA and is an important factor in the pathophysiology of OA (Wang et al., 2015). However, there is often a poor correlation between structural changes to the joint visible on plain radiographs and the level of pain experienced, as observed in a study by Arendt-

Nielsen et al. (2010). The results of this study demonstrated that patients with severe knee pain have a lower pain threshold to pressure stimuli than healthy controls, suggesting the presence of local hypersensitivity in patients with knee OA. The authors also found that individuals with OA of the knee also have impaired descending pain modulation mechanisms and increased temporal pain summation (Arendt-Nielsen et al., 2010). These findings suggest the presence of central sensitization in patients with OA, which may explain the discrepancy between pain intensity and the degree of structural damage to the joint (Arendt-Nielsen et al., 2010). Evidence for the presence of central sensitization in OA patients was also presented in a systematic review by Lluch et al. (2014), who found that CNS hypersensitivity is present in approximately 30 % of OA patients and that central sensitization plays a key role in the pain problems reported by patients. In addition to pathological alterations in joint structures and pain-related neuroplastic changes in the dorsal horn of the spinal cord, which are manifested by the development of central sensitization, the researchers also found that individuals with OA also have alterations in the sensorimotor regions of the CNS. Therefore, in OA, there may be a reorganization of the primary somatosensory (S1) or primary motor cortex (M1), manifested as a change in the somatotopic organization of sensory or motor homunculi (Stanton et al., 2012). Quadriceps muscle weakness, impaired proprioception and altered gait patterns and muscle activation often occur in patients with knee OA (Shanahan et al., 2015). These changes in motor control in patients lead to changes in sensation, which may be due to the aforementioned reorganization of the brain (Shanahan et al., 2015). In their study, Shanahan et al. (2015) investigated the presence of changes in the organization of the motor cortex in patients with knee OA. In individuals with knee osteoarthritis, there was an anterior shift in the representation of the knee and an alternation in the relative anterior-posterior arrangement of the knee and ankle representations, when compared to asymptomatic controls (Shanahan et al., 2015). An anterior shift in the representation of the knee, however, meant a worse performance of the motor task. These findings suggest that motor cortex reorganization is present in knee OA, and raise the possibility that knee OA may also be the origin of plastic motor cortex changes (Shanahan et al., 2015). Stanton et al. (2013) found the presence of a disrupted representation of the knee in the primary somatosensory cortex in individuals with knee OA by assessing tactile acuity measured with a two-point discrimination threshold. The results of their study showed that in individuals with knee OA, compared to healthy controls and individuals with arm pain, the tactile acuity of the knee is decreased. Decreased tactile acuity, however, is a clinical sign for disturbances in the representation of the touch of an individual body part in S1 (Stanton et al., 2013). In another study, Stanton et al. (2012) using the implicit motor imagery task found that individuals with knee OA experience disturbances in the accuracy of this task, namely in a spatially defined manner. Therefore, Stanton et al. (2012) suggest that these disturbances in patients with knee OA may contribute to impaired cortical proprioceptive representation. In their research, Gilpin et al. (2015) also reached similar conclusions as their predecessors. By performing the stretch and shrink illusion created using the Newport MIRAGE multisensory illusion system, they found that in people with painful arm OA, the perceived size of their painful limb was smaller than it actually was, supporting their hypothesis that patients with hand OA have an altered cortical representation of the size of the affected limb (Gilpin et al., 2015). In their review of the literature, Salazar-Méndez et al. (2023) found that in patients with osteoarthritis of the knee, there are pain-related structural and functional changes in the prefrontal cortex, insula, amygdala, anterior cingulate cortex and nucleus accumbens when compared to healthy individuals. These areas of the brain are responsible for comprehensive pain processing (Salazar-Méndez et al., 2023). All this evidence thus demonstrates that neuroplastic changes in the central nervous system occur in patients with OA.

The majority of literature on the rehabilitation and treatment of patients with osteoarthritis (OA) is primarily focused on classical forms of treatment, which predominantly utilise a biomechanical approach and are primarily aimed at addressing pathoanatomical changes in joint structures. There is a paucity of studies on the management of patients with OA that extend beyond a biomechanical approach. The therapies presented in these studies diverge from classical approaches in that they are primarily aimed at the neuroplastic changes of the CNS that are present in patients with OA.

Given the evidence that an important part of the pathophysiology of OA, in addition to structural changes of the affected joint, are also structural and functional changes of the CNS, which influence the formation and experience of symptoms such as pain, it is becoming increasingly important to be aware of such therapies.

One method that extends beyond the biomechanical approach and with which we can achieve CNS desensitization is pain neuroscience education (PNE), which was presented in a systematic review and meta-analysis by Lesmond et al. (2024). Pain neuroscience education is a cognitive-based therapeutic approach that considers the biopsychosocial nature of osteoarthritic pain. The goal of this approach is to enhance the patient's comprehension of pain, the nervous system, and the various factors that can influence pain perception, thereby changing the patient's perception of pain (Lesmond et al., 2024). Some studies indicate that patients with OA frequently adopt a biomedical perspective on OA and associated pain, which can result in kinesiophobia and catastrophizing (Darlow et al., 2018). With the principles of PNE, we can achieve a reconceptualization of these views, which leads to the desensitization of the CNS and, consequently, to the reduction of pain and associated catastrophizing and kinesiophobia, which is also confirmed by the results of a systematic review and meta-analysis by Lesmond et al. (2024). In their recently published experimental study, Caneiro et al. (2023) investigated the efficacy of cognitive functional therapy (CFT) in the treatment of individuals with knee osteoarthritis. The authors of this study started from the fact that in clinical practice it often happens that patients with OA do not respond to classical forms of treatment, such as exercise therapy, education and weight loss, despite their proven effectiveness (Caneiro et al., 2023). In these patients, according to the authors, an individualized approach targeting the many factors contributing to pain and disability, which CFT is, would be necessary. CFT is a behavioral approach that addresses the numerous and varied multidimensional factors that contribute to the experience of pain and disability in individuals with OA (Caneiro et al., 2023). This reinforces the patient's comprehension of the biopsychosocial aspects of their condition and their sense of self-efficacy to perform movements and activities that would otherwise cause them discomfort, which they are reluctant to undertake. This, in turn, enables the patient to effectively self-manage their condition (Caneiro et al., 2023). In a study published by Caneiro et al. (2023), it was found that CFT is an effective method for treating patients with OA. The study participants were observed to have two distinct responses to therapy: one demonstrating a clear shift towards a biopsychosocial understanding of OA and its management, and the other showing a mixed conceptualization of OA with inconsistent beliefs about the disease (Caneiro et al., 2023). The authors hypothesize that this latter response may be influenced by individual psychological and social factors. Based on clinical evidence indicating that altered cortical representations of the body during pain may be linked to the perception of pain, Stanton et al. (2018) conducted a proof-of-concept study to determine whether visuotactile illusions that change the perceived size of the knee have an analgesic effect in individuals with painful knee OA. The results of the study demonstrated that illusory knee resizing has an analgesic effect in individuals with knee osteoarthritis (Stanton et al., 2018). In addition, the results showed that the visual component plays a key role in visuo-tactile illusions, but multisensory input is required to achieve analgesia (Stanton et al., 2018). The findings of this study contribute to the existing body of research indicating that modifying sensory information relevant to the body can influence pain perception (Stanton et al., 2018). Furthermore, the authors highlight the necessity for additional research to investigate the neural background of these visuo-tactile illusions in more detail, and that before the possible clinical implementation of this method in the physiotherapeutic treatment of patients with OA, further studies on larger samples of included subjects are needed (Stanton et al., 2018). The graded motor imagery (GMI) has been demonstrated to target pain-related structural and functional changes in the sensorimotor areas of the brain in individuals with OA. This conclusion was reached by Galonski et al. (2023) in their systematic review and meta-analysis, which also indicated that the GMI could be an effective method for reducing pain, kinesiophobia and disability in individuals with OA. Graded motor imagery is a multimodal method that comprises three stages: (1) implicit motor imagery, (2) explicit motor imagery and (3) mirror therapy with which we can improve the cortical organization of sensorimotor areas in patients by

gradually activating cortical motor networks brain and thus reduce pain (Priganc & Stralka, 2011). However, despite the positive effects found in reducing pain and kinesiophobia in knee OA patients, Galonski et al. (2023) emphasize that further high-quality controlled studies with a larger sample of subjects are needed to make definitive recommendations regarding the implementation of GMI in the management of patients with OA. With different approaches, we can also upgrade exercise therapy, which clinical guidelines classify as one of the most effective methods in the treatment of patients with OA. Virtual reality (VR) can be integrated into exercise therapy. The mechanisms of action of virtual reality training were described in a systematic review and meta-analysis by Wei et al. (2024). By stimulating somatosensory, motor, visual and auditory networks, VR exercise changes pain perception and increases the activity of those areas of the CNS that are associated with pain inhibition (Wei et al., 2024). By modulating descending pain control systems, VR exercise shifts attention away from pain, thereby influencing pain perception (Wei et al., 2024). Wei et al. (2024) found that VR exercise therapy was effective in reducing pain in individuals with knee OA. The results of the study demonstrated that the immersive VR method has a more pronounced impact on pain reduction than the non-immersive VR method. This is because the non-immersive method results in a lower level of sensory substitution, which in turn leads to a greater perception of pain. In contrast, exercising with the immersive VR method reduces attention to pain perception (Wei et al., 2024). The authors propose that one potential physiological mechanism through which VR exercise may enhance functional performance is increased dopamine release in the striatum, which contributes to enhanced attention and facilitates sensorimotor integration (Wei et al., 2024). The stimulation of proprioceptors through sensorimotor integration facilitates the restoration of muscle strength in the knee joint, thereby enhancing its functionality and stability (Wei et al., 2024). By gamifying the environment for the patient, virtual reality also creates a more attractive environment for exercise (Wei et al., 2024). In addition, VR exercise through the activation of sensory functions in patients with knee OA restores movement capacity, which further improves the functional disability of patients (Wei et al., 2024). The results of this study also showed that VR exercise improves muscle strength, which is crucial for OA patients, as strong muscles ensure joint stability (Wei et al., 2024). Exercise therapy can also be upgraded with the principles of behaviorally graded activity (BGA), which was described in study published by Veenhof et al. (2006). Behavioral graded activity is a behavior-oriented therapy that incorporates the principles of operant and temporal conditioning. These principles facilitate the reinforcement of healthy behaviors in OA patients, thereby diverting their attention away from pain and pain-related behaviors. This, in turn, increases the patient's activity level in a time-dependent manner (Veenhof et al., 2006). Pisters et al. (2010) found that, compared to classical forms of physiotherapeutic treatment, behavioral graded activity in patients with OA of the knee and hip increases their physical activity in the short and long term and ensures greater involvement in exercise therapy. Including various forms of exercise therapy in the process of physiotherapeutic treatment of patients with OA and increasing their daily activity is not only important from the point of view of increasing muscle strength and the resulting improvement of joint stabilization and its biomechanics (Helmark et al., 2010). The results of a systematic review and meta-analysis conducted by Puts et al. (2023), showed that various forms of exercise therapy in patients with knee OA trigger circulatory and intra-articular anti-inflammatory effects and can therefore be an effective method in managing both local and systemic inflammation, which are important factors in the pathophysiology of OA.
Based on the results of our research, we can say that osteoarthritis is a disease with a complex pathophysiology that allows for different forms of treatment that go beyond a purely biomechanical approach.

CONCLUSION

Osteoarthritis is a disease with a complex pathophysiology in which mechanical as well as inflammatory and metabolic factors play an important role, acting on a local and systemic level and causing structural changes in the entire joint. In the last decade, researchers have also come to the realization that the formation and experience of pain, which is the most limiting symptom for patients with OA, is not only influenced by pathoanatomical changes in joint structures, but also by neuroplastic changes in the dorsal horn of the spinal cord and higher regions of the central nervous system, which are responsible for processing pain. These insights thus significantly change and influence the choice of methods and techniques involved in the physiotherapeutic treatment of patients with osteoarthritis. When treating patients with OA, despite their proven effectiveness, physiotherapists should not rely solely on classical forms of treatment such as exercise therapy, education, weight loss and manual therapy, as these often do not achieve the desired results in patients with neuroplastic changes of the CNS because they are mainly directed at the joint and its surrounding structures. Therefore, in addition to classical methods, it is recommended to include methods that focus on changes within the central nervous system in the treatment of patients with OA. In the physiotherapeutic treatment of patients with OA, we therefore recommend the use of methods such as pain neuroscience education, cognitive behavioral therapy, graded motor imagery, virtual reality exercise, behavioral graded activity and various forms of exercise therapy that also focus on changes within the central nervous system and go beyond a purely biomechanical approach. Since most of the mentioned methods for the treatment of patients with OA are still under development, further high-quality studies on larger samples of included subjects are needed to determine their utility and effectiveness in the physiotherapy treatment of patients with OA. Therefore, it should be emphasized at this point that the described recommendations are only indicative in nature. Nevertheless, they clearly show us that, in addition to the classically used methods and techniques, physiotherapists also have new innovative methods at their disposal, with which we can upgrade and improve the physiotherapeutic treatment of patients with OA, thereby significantly contributing to the relief of OA-related symptoms and to improving the quality of life of patients with OA.

REFERENCES

1. Abramoff, B., & Caldera, F. E. (2020). Osteoarthritis: Pathology, Diagnosis, and Treatment Options. *The Medical Clinics of North America*, *104*(2), 293–311. https://doi.org/10.1016/j.mcna.2019.10.007
2. Arendt-Nielsen, L., Nie, H., Laursen, M. B., Laursen, B. S., Madeleine, P., Simonsen, O. H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain*, *149*(3), 573–581. https://doi.org/10.1016/j.pain.2010.04.003
3. Caneiro, J. P., O'Sullivan, P., Tan, J.-S., Klem, N.-R., de Oliveira, B. I. R., Choong, P. F., Dowsey, M., Bunzli, S., & Smith, A. (2023). Process of change for people with knee osteoarthritis undergoing cognitive functional therapy: A replicated single-case experimental design study. *Disability and Rehabilitation*, *0*(0), 1–17. https://doi.org/10.1080/09638288.2023.2221459
4. Darlow, B., Brown, M., Thompson, B., Hudson, B., Grainger, R., McKinlay, E., & Abbott, J. H. (2018). Living with osteoarthritis is a balancing act: An exploration of patients' beliefs about knee pain. *BMC Rheumatology*, *2*, 15. https://doi.org/10.1186/s41927-018-0023-x
5. Fang, T., Zhou, X., Jin, M., Nie, J., & Li, Xi. (2021). Molecular mechanisms of mechanical load-induced osteoarthritis. *International Orthopaedics*, *45*(5), 1125–1136. https://doi.org/10.1007/s00264-021-04938-1
6. Fu, K., Robbins, S. R., & McDougall, J. J. (2018). Osteoarthritis: The genesis of pain. *Rheumatology (Oxford, England)*, *57*(suppl_4), iv43–iv50. https://doi.org/10.1093/rheumatology/kex419
7. Galonski, T., Mansfield, C., Moeller, J., Miller, R., Rethman, K., & Briggs, M. S. (2023). Does graded motor imagery benefit individuals with knee pain: A systematic review and meta-analysis. *Journal of Bodywork and Movement Therapies*, *35*, 130–139. https://doi.org/10.1016/j.jbmt.2023.05.005
8. Gilpin, H. R., Moseley, G. L., Stanton, T. R., & Newport, R. (2015). Evidence for distorted mental representation of the hand in osteoarthritis. *Rheumatology (Oxford, England)*, *54*(4), 678–682. https://doi.org/10.1093/rheumatology/keu367
9. Goldring, M. B., Culley, K. L., & Otero, M. (2017). Pathogenesis of Osteoarthritis in General. In S. Grässel & A. Aszódi (Eds.), *Cartilage: Volume 2: Pathophysiology* (pp. 1–25). Springer International Publishing. https://doi.org/10.1007/978-3-319-45803-8_1

10. Helmark, I. C., Mikkelsen, U. R., Børglum, J., Rothe, A., Petersen, M. C. H., Andersen, O., Langberg, H., & Kjaer, M. (2010). Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: A randomized controlled trial. *Arthritis Research & Therapy*, *12*(4), R126. https://doi.org/10.1186/ar3064
11. Holden, M. A., Nicolson, P. J. A., Thomas, M. J., Corp, N., Hinman, R. S., & Bennell, K. L. (2023). Osteoarthritis year in review 2022: Rehabilitation. *Osteoarthritis and Cartilage*, *31*(2), 177–186. https://doi.org/10.1016/j.joca.2022.10.004
12. Hunter, D. J., & Bierma-Zeinstra, S. (2019). Osteoarthritis. *Lancet (London, England)*, *393*(10182), 1745–1759. https://doi.org/10.1016/S0140-6736(19)30417-9
13. Kolasinski, S. L., Neogi, T., Hochberg, M. C., Oatis, C., Guyatt, G., Block, J., Callahan, L., Copenhaver, C., Dodge, C., Felson, D., Gellar, K., Harvey, W. F., Hawker, G., Herzig, E., Kwoh, C. K., Nelson, A. E., Samuels, J., Scanzello, C., White, D., … Reston, J. (2020). 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Care & Research*, *72*(2), 149–162. https://doi.org/10.1002/acr.24131
14. Lesmond, I., Calvache-Mateo, A., Heredia-Ciuró, A., Martín-Núñez, J., Navas-Otero, A., López-López, L., & Valenza, M. C. (2024). Neurophysiological pain education for patients with symptomatic knee osteoarthritis: A systematic review and meta-analysis. *Patient Education and Counseling*, *120*, 108128. https://doi.org/10.1016/j.pec.2023.108128
15. Lluch, E., Torres, R., Nijs, J., & Van Oosterwijck, J. (2014). Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *European Journal of Pain (London, England)*, *18*(10), 1367–1375. https://doi.org/10.1002/j.1532-2149.2014.499.x
16. O'Neill, T. W., & Felson, D. T. (2018). Mechanisms of Osteoarthritis (OA) Pain. *Current Osteoporosis Reports*, *16*(5), 611–616. https://doi.org/10.1007/s11914-018-0477-1
17. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71
18. Pisters, M. F., Veenhof, C., de Bakker, D. H., Schellevis, F. G., & Dekker, J. (2010). Behavioural graded activity results in better exercise adherence and more physical activity than usual care in people with osteoarthritis: A cluster-randomised trial. *Journal of Physiotherapy*, *56*(1), 41–47. https://doi.org/10.1016/s1836-9553(10)70053-9
19. Priganc, V. W., & Stralka, S. W. (2011). Graded motor imagery. *Journal of Hand Therapy: Official Journal of the American Society of Hand Therapists*, *24*(2), 164–168; quiz 169. https://doi.org/10.1016/j.jht.2010.11.002
20. Puts, S., Liberman, K., Leysen, L., Forti, L., Muyldermans, E., Vaes, P., Nijs, J., Beckwée, D., & Bautmans, I. (2023). Exercise-induced effects on inflammatory markers and brain-derived neurotrophic factor in patients with knee osteoarthritis. A systematic review with meta-analysis. *Exercise Immunology Review*, *29*, 22–53.
21. Roos, E. M., Grønne, D. T., Thorlund, J. B., & Skou, S. T. (2022). Knee and hip osteoarthritis are more alike than different in baseline characteristics and outcomes: A longitudinal study of 32,599 patients participating in supervised education and exercise therapy. *Osteoarthritis and Cartilage*, *30*(5), 681–688. https://doi.org/10.1016/j.joca.2022.02.001
22. Salazar-Méndez, J., Cuyul-Vásquez, I., Viscay-Sanhueza, N., Morales-Verdugo, J., Mendez-Rebolledo, G., Ponce-Fuentes, F., & Lluch-Girbés, E. (2023). Structural and functional brain changes in people with knee osteoarthritis: A scoping review. *PeerJ*, *11*, e16003. https://doi.org/10.7717/peerj.16003
23. Sellam, J., & Berenbaum, F. (2013). Is osteoarthritis a metabolic disease? *Joint Bone Spine*, *80*(6), 568–573. https://doi.org/10.1016/j.jbspin.2013.09.007
24. Shanahan, C. J., Hodges, P. W., Wrigley, T. V., Bennell, K. L., & Farrell, M. J. (2015). Organisation of the motor cortex differs between people with and without knee osteoarthritis. *Arthritis Research & Therapy*, *17*(1), 164. https://doi.org/10.1186/s13075-015-0676-4

25. Stanton, T. R., Gilpin, H. R., Edwards, L., Moseley, G. L., & Newport, R. (2018). Illusory resizing of the painful knee is analgesic in symptomatic knee osteoarthritis. *PeerJ*, *6*, e5206. https://doi.org/10.7717/peerj.5206
26. Stanton, T. R., Lin, C.-W. C., Bray, H., Smeets, R. J. E. M., Taylor, D., Law, R. Y. W., & Moseley, G. L. (2013). Tactile acuity is disrupted in osteoarthritis but is unrelated to disruptions in motor imagery performance. *Rheumatology (Oxford, England)*, *52*(8), 1509–1519. https://doi.org/10.1093/rheumatology/ket139
27. Stanton, T. R., Lin, C.-W. C., Smeets, R. J. E. M., Taylor, D., Law, R., & Lorimer Moseley, G. (2012). Spatially defined disruption of motor imagery performance in people with osteoarthritis. *Rheumatology (Oxford, England)*, *51*(8), 1455–1464. https://doi.org/10.1093/rheumatology/kes048
28. Sun, H. B. (2010). Mechanical loading, cartilage degradation, and arthritis. *Annals of the New York Academy of Sciences*, *1211*, 37–50. https://doi.org/10.1111/j.1749-6632.2010.05808.x
29. Veenhof, C., Köke, A. J. A., Dekker, J., Oostendorp, R. A., Bijlsma, J. W. J., van Tulder, M. W., & van den Ende, C. H. M. (2006). Effectiveness of behavioral graded activity in patients with osteoarthritis of the hip and/or knee: A randomized clinical trial. *Arthritis and Rheumatism*, *55*(6), 925–934. https://doi.org/10.1002/art.22341
30. Wang, X., Hunter, D., Xu, J., & Ding, C. (2015). Metabolic triggered inflammation in osteoarthritis. *Osteoarthritis and Cartilage*, *23*(1), 22–30. https://doi.org/10.1016/j.joca.2014.10.002
31. Wei, W., Tang, H., Luo, Y., Yan, S., Ji, Q., Liu, Z., Li, H., Wu, F., Yang, S., & Yang, X. (2024). Efficacy of virtual reality exercise in knee osteoarthritis rehabilitation: A systematic review and meta-analysis. *Frontiers in Physiology*, *15*, 1424815. https://doi.org/10.3389/fphys.2024.1424815