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Review Article

Beyond movement: exploring the combined impact of breathing exercises and the PEPSMAN protocol on cognitive and functional recovery in knee osteoarthritis

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ABSTRACT

Knee Osteoarthritis (KOA), a leading cause of disability globally, is linked to sedentary lifestyles, obesity, and chronic low-grade inflammation affecting joint and cognitive health. Physical exercise reduces oxidative stress and inflammation, benefiting brain health. The PEPSMAN protocol—combining patient education, exercise, and manual therapy—improves balance, pain, physical function, and reduces disability in KOA. Although limited, early evidence suggests combining PEPSMAN with breathing exercises offers additional benefits. This review synthesizes recent research on the interplay of inflammation, cognition, pain, and rehabilitation in Grade II–III KOA. A comprehensive search across databases like EMBASE, SCOPUS, DOAJ, PubMed, Google Scholar, and Web of Science identified peer-reviewed articles and clinical trials focusing on these factors in KOA.KOA progression associates with increased dementia and Alzheimer's disease risk; chronic pain significantly contributes to cognitive decline and functional impairment. Emerging studies reveal respiration influences cognitive performance. Combining breathing exercises with PEPSMAN enhances cognition and physical function in KOA by reducing inflammation, improving autonomic regulation, and promoting neuroplasticity, addressing joint symptoms and cognitive decline in a holistic approach. Chronic low-grade inflammation is central to KOA pathophysiology, driving joint damage and neurodegeneration linked to cognitive decline and Alzheimer's disease risk. This highlights the need for integrative management targeting musculoskeletal and neurocognitive health.

Keywords: Breathing exercises, Cognitive decline, Grade II and grade III knee osteoarthritis, PEPSMAN protocol, Physical therapy, Rehabilitation

INTRODUCTION

Osteoarthritis (OA) is recognized as one of the leading causes of disability worldwide, with the knee joint being the most commonly affected site. This chronic degenerative disorder is characterized by gradual deterioration of articular cartilage, inflammation of the synovial membrane, and alterations in the subchondral bone structure. These pathological changes result in pain, joint stiffness, and limited mobility, which significantly diminish individuals' functional independence and quality of life. Given its increasing prevalence and profound impact on public health, OA presents a major challenge for healthcare systems globally, necessitating focused prevention and management strategies.[1,2] India faces a significant challenge with OA, with prevalence rates estimated to range from 22% to as high as 47% among various populations, particularly in the elderly. These rates are notably higher than those reported in many Western countries. The increasing burden is driven by

factors such as rapid urbanization, changing lifestyles, rising obesity, and an aging population. This growing prevalence underscores an urgent need for effective public health strategies to manage OA and reduce its impact on individuals' mobility, independence, and quality of life in resource-limited settings like India.[3] The rising global burden of knee OA is closely linked to increasingly sedentary lifestyles and growing rates of obesity. These factors not only put extra mechanical stress on the knee joints, accelerating cartilage damage, but also trigger chronic low-grade inflammation. This inflammation is driven by substances released from fat tissue—called adipokines and proinflammatory cytokines—which worsen disease progression and symptoms. Because of their strong influence, lifestyle factors like physical activity and weight management are now seen as key players in both the development and worsening of OA. Addressing these modifiable risks is crucial for improving outcomes and quality of life for those affected by OA.[4,5]

OA has traditionally been viewed as a condition affecting only the joints, but recent research shows it involves systemic inflammation that impacts the whole body. This chronic, low-level inflammation is linked not only to joint damage but also to broader health issues, including cognitive decline and an increased risk of diseases like Alzheimer's. Inflammation-related molecules circulating in the blood can trigger inflammation in the brain, weaken the blood-brain barrier, and potentially speed up nerve cell damage. Understanding OA as a systemic inflammatory disease highlights the need for comprehensive approaches to treatment that consider both joint health and overall well-being, especially in community health settings.[6,7] Managing OA effectively today means taking a whole-person approach. It's not enough to just focus on controlling pain and improving joint movement with medications, exercise, or surgery. We also need to consider lifestyle factors that patients can change, like diet and activity level, as well as the complex ways OA affects the body beyond the joints. Traditional treatments remain essential, but they often miss addressing important areas like mental health and cognitive function, which play a big role in how well patients do overall. By combining medical care with support for psychological well-being and healthy living, healthcare providers can offer more complete, personalized care that truly improves quality of life for people with OA.[8,9] Research shows that treating OA is more effective when mind–body approaches and combined therapies are used, rather than just relying on exercise or therapy alone. Meta-analyses reveal that regular aerobic or resistance exercise by itself may not significantly improve depression in OA patients. However, approaches like yoga, tai chi, and qigong that blend physical activity with mental focus provide better relief from both pain and depressive symptoms. This highlights the importance of incorporating holistic and multimodal treatments to improve overall well-being for those living with OA.[10] OA and neurodegenerative diseases like Alzheimer's share several underlying pathological features. Research shows that chronic pain from OA is linked to neuroinflammation, disruption of synaptic connections, and specific loss of brain tissue. These changes primarily affect brain areas involved in decision-making, memory, and emotional control, such as the prefrontal cortex, hippocampus, and parahippocampal regions. Notably, the hippocampus—a critical area for learning and emotions—undergoes faster shrinkage in people with persistent pain conditions like OA, highlighting the complex relationship between long-term pain, cognitive decline, and brain aging. Understanding these connections can open new avenues for integrated care approaches that address both joint health and brain function in affected individuals.[11-13] Many studies have proven that physical exercise in older adults can improve cognition and made a statement that the vascular and neural adaptations to physical exercise improve cognitive function through promotion of angiogenesis, neurogenesis, decreased proinflammatory processes, synaptic plasticity and reduced cellular damage due to oxidative stress.[14] A clinical trial of exercise training showed that hippocampal volume losses in late adulthood are avoidable and reversible with moderate-intensity exercise. It also helps reduce oxidative stress and inflammation, which can damage brain tissue. These effects can stop or even reverse the shrinking of the hippocampus, a brain area crucial for memory, and slow down the mental decline that comes with aging. This highlights the important role of an active lifestyle in maintaining brain health and cognitive function in older age.[15]

The PEPSMAN physiotherapy protocol, which combines patient education, exercise therapy, and manual therapy, has been shown to significantly improve static and dynamic balance, reduce pain, enhance physical function, and decrease disability in patients with knee OA. Data collected after four weeks of intervention clearly demonstrate these positive outcomes. However, aging appears to slow the therapeutic benefits, likely due to age-related changes such as cell aging altered cell death, mitochondrial dysfunction, oxidative stress, and disrupted tissue balance all which contribute to OA progression.[16] Recent studies highlight the important role of breathing exercises in brain health. These exercises have been shown to improve oxygen flow to the brain, help balance the autonomic nervous system, and activate brain areas responsible for attention, emotional control, and memory. As a result, practicing controlled breathing can boost cognitive function and mental performance. This growing evidence points to breathing techniques as a simple yet powerful tool to support brain health and enhance cognitive abilities.[14] Although research specifically combining physiotherapy protocols like the PEPSMAN approach with breathing exercises in OA is still limited, early findings and experience from similar rehabilitation settings suggest these methods together can have added benefits. Combining physical therapy with breathing exercises may work together to improve both cognition

and physical function more effectively than either alone. This potential synergy highlights a promising area for further investigation to enhance holistic care for OA patients in the community.[17] This review brings together the latest research on how inflammation, thinking skills, pain, and new rehabilitation methods—including the PEPSMAN protocol and breathing exercises—interact in knee osteoarthritis (KOA). It highlights how these strategies may help slow cognitive decline and improve both mental and physical function for those living with knee OA. Understanding this connection can help guide more effective, holistic treatment approaches in community care settings.

METHODS

This section outlines the methodological approach for this narrative review, detailing the search strategy, inclusion and exclusion criteria for selecting relevant literature, and the framework used for synthesizing the gathered evidence. A comprehensive search was conducted across major electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify peer-reviewed articles, reviews, and clinical trials published up to the present date. Keywords used in the search included "KOA," "cognitive function," "pain," "breathing exercises," "respiratory training," "PEPSMAN protocol," "neuropathology," "neuroinflammation," "neuroplasticity," and "functional outcomes." The search aimed to identify studies that specifically investigated the interplay between these factors in Grade II–III KOA. Additionally, manual searches of reference lists from included articles and relevant systematic reviews were performed to ensure comprehensive coverage of the literature. Inclusion criteria focused on studies published in English that addressed human subjects diagnosed with Grade II–III KOA, exploring cognitive function, pain management, breathing interventions, or the PEPSMAN protocol. Studies focusing solely on surgical interventions, animal models, or other grades of OA were excluded to maintain specificity and relevance to the review's objectives. Thematic analysis was employed to synthesize findings, focusing on the intricate relationships between cognitive impairment, pain mechanisms, and the efficacy of breathing exercises within the context of the PEPSMAN protocol for Grade II-III KOA.

RESULTS

Analysis of the literature highlights several critical themes regarding the pathophysiology of KOA, its relationship to cognitive outcomes, and the comparative efficacy of available interventions. Neuroimaging and neurophysiological research consistently demonstrate that individuals with KOA experience distinct cognitive deficits, particularly in global cognition and attention, which are accompanied by measurable alterations in specific brain regions such as the hippocampal subfields and the prefrontal cortex.[12-18] Chronic low-grade inflammation emerges as a central pathway linking KOA to cognitive decline, with elevated peripheral inflammatory markers (e.g., serum TIM-3, interferon-gamma) correlating with reduced hippocampal volume and diminished performance on cognitive tests.[19] The bone-brain axis model suggests that peripheral joint pathology initiates neuroimmune cascades, driving central nervous system changes associated with accelerated brain aging and memory loss.[20]

Clinical observations further reveal that the progression of KOA is associated with an increased risk of all-cause dementia and Alzheimer's disease, with chronic pain significantly contributing to cognitive decline and functional impairment. Meta-analyses and controlled studies indicate that domain-specific memory loss and executive dysfunction are predominant cognitive symptoms among older adults with KOA.[18] Visuospatial ability and planning in 70% of the population is impaired and, 38 % report problems with attention and mental flexibility.[21,22]

Additionally, evidence supports the use of multimodal interventions, including integrated physical and mind–body approaches, for improving pain, mood, and physical function beyond what unimodal therapies can achieve. Patients receiving such interventions report superior outcomes in pain relief and psychological health, and some studies suggest that approaches like knee arthroplasty may help preserve cognitive function in advanced cases.[23-25]

PEPSMAN physiotherapy protocol i.e., combination of patient education, exercise therapy and manual therapy is an already registered protocol and was found to have a significant therapeutic role in improvement of static balance, dynamic balance, pain, physical functional performance, and disability in patients with KOA. The PEPSMAN intervention data of the samples collected after four weeks clearly shows the outcome.[14-16]

Many studies have proven that physical exercise in older adults can improve cognition.[26] According to the American College of Sports Medicine's guidelines a minimum of 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity activity per week is prescribed.[27] Studies shows results for moderate intensity exercise of 150 minutes per week are helpful in improving cognition in elder adults.[26]

Recent scientific study, on the other hand, has shown that respiration has an influence on cognitive performance. Conscious control of breathing and Breathing techniques such as deep diaphragmatic breathing, alternative nostril breathing, and slow breathing have gained popularity due to their ability to increase overall brain function, cognitive performance, and stress reduction.[28-31]

DISCUSSION

This review synthesizes the current literature to elucidate the role of breathing exercises as an adjunct to the

PEPSMAN physiotherapy protocol in enhancing cognition and functional ability in patients with Grade II and Grade III KOA. The collective evidence reflects a complex and evolving understanding of KOA as a systemic condition with far-reaching implications beyond localized joint pathology, including chronic inflammation, cognitive decline, and neurophysiological alterations. Chronic low-grade inflammation, a hallmark of KOA, underpins both joint degeneration and cognitive impairments. Umoh et al highlighted molecular links connecting OA with Alzheimer's disease (AD), demonstrating that elevated proinflammatory cytokines such as TNF-α and IL-1β contribute to cartilage degradation and trigger neuroinflammatory cascades. These cytokines compromise the blood-brain barrier, activate microglial cells, and promote neurodegeneration, elucidating the mechanistic pathways through which KOA may predispose to cognitive decline and neurodegenerative diseases like AD. Persistent systemic inflammation exacerbates central nervous system pathology, including amyloid-beta aggregation and tau hyper phosphorylation, further linking OA with dementia risk.[26] Epidemiological studies, such as that by Shimada et al, reveal that cognitive decline in OA manifests across multiple cognitive domains—memory, attention, executive function, and decision-making—thereby significantly impairing patients' daily functioning and quality of life.[32]

Physical exercise has emerged as a cornerstone intervention for mitigating both the musculoskeletal and cognitive sequelae of OA. Mechanistic studies have shown that exercise promotes neuroprotective processes—neurogenesis, angiogenesis, synaptic plasticity—while reducing oxidative stress and systemic inflammation, thereby counteracting cognitive decline associated with aging and chronic disease. Complementing exercise, controlled breathing techniques such as deep diaphragmatic and alternate nostril breathing have been demonstrated to enhance cerebral oxygenation, reduce psychological stress, and improve mental clarity and cognitive performance. This synergy suggests that integrating conscious respiration practices with physical activity protocols may yield additive or even synergistic benefits for cognition and physical function among KOA patients.[33-35]

The PEPSMAN protocol—comprising patient education, progressive resistance exercise, passive stretching, soft tissue manipulation, muscle energy techniques, Maitland mobilization, aerobic exercises, and neuromuscular training—has been validated in Indian clinical cohorts to significantly reduce pain, enhance static and dynamic balance, improve physical functional performance, and reduce disability in KOA patients.[14,16] While aging-related cellular alterations—mitochondrial dysfunction, oxidative stress, and apoptosis—may modulate the response rate, favorable outcomes with PEPSMAN persist across the lifespan. This underscores the protocol's suitability as a non-pharmacological therapeutic approach adaptable to diverse KOA populations.[14]

Neurophysiological research offers granular insights into the mechanisms linking chronic KOA pain with cognitive decline. Neuroimaging studies consistently report atrophy and altered connectivity in key brain regions implicated in cognition and emotion regulation, including the prefrontal cortex, hippocampus, insula, and anterior cingulate cortex (Patel et al, Lin et al and Johnson et al).[36-38] These neural changes corroborate the observed executive dysfunction, memory impairments, and attention deficits in KOA patients and support the neural resource hypothesis whereby chronic pain continuously diverts cognitive processing resources, accelerating neural aging. Moreover, altered functional connectivity in the default mode network and limbic circuitry further disrupts cognitive and emotional homeostasis, establishing chronic KOA as a brain-body disorder.

Adding a compelling neurophysiological dimension, Heck et al revealed that respiratory rhythms actively modulate large-scale brain activity and neural oscillations critical for cognition and emotional regulation. Specifically, the rhythmic breathing cycle entrains oscillatory activity in the olfactory bulb, hippocampus, amygdala, and prefrontal cortex, synchronizing neuronal firing patterns through hippocampal theta rhythms to optimize memory encoding and retrieval. Nasal breathing exerts particularly potent effects, enhancing this respiratory-brain coupling and facilitating superior cognitive performance. Respiratory signals conveyed via the vagus nerve to brainstem nuclei influence cortical and limbic circuits, modulating autonomic balance, attention and executive function key cognitive domains compromised in KOA.[39]

Neuroplasticity induced by breath control training fosters increased gray matter density and functional activity in cognitive-related regions including the prefrontal cortex, anterior cingulate cortex, and hippocampus. These changes underpin improved attention, memory, and emotional regulation observed in clinical and healthy populations engaging in breathing exercises (Heck et al).[39] Integrating such targeted breathing techniques into the PEPSMAN physiotherapy framework offers a multimodal approach that addresses both peripheral joint pathology and central nervous system dysfunction, optimizing outcomes across physical, cognitive, and psychological domains.

In practical terms, combining structured physiotherapy regimens like PEPSMAN with conscious breathing exercises can yield superior clinical benefits. Existing studies suggest that such integrative protocols reduce joint pain, stiffness, and functional limitations while enhancing psychological well-being and quality of life. Improved heart rate variability—the biomarker of autonomic nervous system balance—reflects enhanced parasympathetic activity and systemic anti-inflammatory

effects, crucial for mitigating the chronic inflammatory state inherent to KOA (Rizvi et al, and Umoh et al).[9,26]

Furthermore, brain regions activated during new perceptual-motor skill development overlap with those modulated by slow, deep breathing, including the limbic system, cerebral motor cortex, post-parietal cortex, prefrontal cortex, and central sulcus. These areas govern complex cognitive processes—thought, perception, executive memory, procedural learning, emotion, and attention—providing further mechanistic evidence linking respiration-based interventions to cognitive enhancement in KOA. Taken together, these data emphasize the necessity of a multidisciplinary approach in KOA management, especially for elderly populations where both physical impairments and cognitive decline prevail. Holistic interventions integrating PEPSMAN with regular physical activity and breathing techniques can substantially improve patients' functional independence and quality of life.

CONCLUSION

OA, particularly KOA, is increasingly recognized as a systemic disorder with multifaceted consequences extending beyond joint degeneration to include significant cognitive and neurological implications. Chronic low-grade inflammation remains central to KOA pathophysiology, driving both peripheral joint damage and central neurodegenerative processes that contribute to cognitive decline and increase the risk for conditions such as Alzheimer's disease. This emerging understanding underscores the necessity for comprehensive and integrative management strategies targeting not only musculoskeletal symptoms but also neurocognitive vulnerabilities.

Interventions combining structured physical exercise, controlled breathing techniques, and physiotherapeutic protocols like the PEPSMAN method hold promising therapeutic potential. Such approaches simultaneously address physical limitations and cognitive dysfunctions prevalent in KOA, which is especially crucial for aging populations disproportionately affected by these dual burdens. Evidence supports the role of physical activity in enhancing neurogenesis, synaptic plasticity, and cognitive resilience, while breathing exercises exert favorable effects on cerebral oxygenation, autonomic regulation, and stress reduction—factors that synergistically improve cognitive and functional outcomes.

The PEPSMAN physiotherapy protocol, encompassing patient education, progressive exercise, manual therapy, aerobic conditioning, and neuromuscular training, has demonstrated efficacy in improving pain, balance, physical function, and disability in KOA patients. When augmented with targeted breathing exercises, this holistic regimen extends therapeutic benefits to cognitive-emotional domains through modulation of neurophysiological pathways, particularly via respiratory-brain coupling mechanisms that facilitate neural synchronization in memory and executive function centers.

Future scope

Future research must prioritize large-scale, randomized controlled trials to rigorously evaluate the synergistic effects of combining breathing exercises with the PEPSMAN protocol on cognitive and functional parameters. Investigations should also examine how these interventions can be optimized for diverse patient populations, including those with varying disease severities, comorbidities, and demographic characteristics. Additionally, mechanistic studies exploring the underlying cellular and neural adaptations induced by integrated therapies will further refine treatment personalization. In summary, the integration of targeted breathing exercises with established physiotherapy protocols such as PEPSMAN represents a forward-thinking, multimodal strategy for managing Grade II–III KOA. By bridging somatic and cognitive domains and emphasizing autonomic nervous system regulation, this approach holds considerable promise for improving both physical function and cognitive health, ultimately enhancing quality of life and independence in individuals affected by OA.

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