UNIVERSITA' DEGLI STUDI DI ROMA "FORO ITALICO"

Department of Movement, Human and Health Science

PhD in Human Movement and Sport Sciences

"Sensorimotor Training and Pain Modulation: Clinical and Functional Insights from Osteoarthritis and Fibromyalgia"

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Contents

Abstract

Chronic musculoskeletal pain represents a major health burden, often leading to disability, psychological distress, and reduced quality of life. Within the modern biopsychosocial framework, chronic pain is understood as a complex and multidimensional phenomenon, arising from the interaction between peripheral nociceptive inputs, central nervous system sensitization, and psychosocial factors. Osteoarthritis (OA) and fibromyalgia (FM) are two paradigmatic chronic pain conditions situated at different points along the nociceptive and nociplastic continuum, sharing common features such as altered pain modulation, reduced physical function, and kinesiophobia.

Adapted physical exercise is recognized as a cornerstone of non-pharmacological pain management. In particular, sensorimotor training, which integrates proprioceptive stimulation, and motor and balance control, may represent a promising approach to restore motor function, enhance body awareness, and modulate pain. Despite its potential, this exercise modality remains underexplored in chronic pain populations.

The present doctoral thesis aimed to explore the clinical, functional, and biological effects of sensorimotor exercise in chronic pain, through a multimodal and translational approach. The work includes: (1) a systematic review and meta-analysis examining the effects of different exercise modalities on pain, functional capacity, and inflammatory biomarkers in OA; (2) one experimental study comparing a 24-week Gyrokinesis® program with Pilates in women with OA, focusing on: (2a) functional and clinical parameter and (2b) exploratory biochemical outcomes; and (3) a pilot study assessing the feasibility of a 12-week sensorimotor training intervention on women affected by FM.

The meta-analysis revealed that neuromuscular and sensorimotor-based interventions produced the largest effect size for pain reduction in OA, compared to aerobic or resistance training. Results from the experimental studies showed that Gyrokinesis® training led to greater improvements in postural control, functional performance, and pain reduction than Pilates, suggesting a specific role of movement quality and proprioceptive engagement. In the exploratory biomarker analysis, Gyrokinesis® elicited an increase in total glutathione and a mild reduction in LDH, indicating potential modulation of oxidative balance. The pilot study confirmed the feasibility, safety, and acceptability of sensorimotor exercise for FM patients, with preliminary improvements in pain, symptoms, sleep quality, and functional capacity.

Together, these findings support the relevance of sensorimotor exercise as an integrative therapeutic strategy for chronic pain conditions. Beyond the mechanical aspects of training, the emphasis on body awareness, rhythmic coordination, and central sensory-motor integration may contribute to pain

modulation through both peripheral and central pathways. This thesis thus contributes to the emerging paradigm that movement quality matters, offering new perspectives for the design of personalized, biopsychosocial exercise interventions in chronic pain rehabilitation.

Keywords: Sensorimotor training; Chronic pain; Osteoarthritis; Fibromyalgia; Exercise therapy; Pain modulation; Movement quality; Biomarkers.

CHAPTER 1

Review of the literature

This chapter aims at reviewing the current literature concerning pain, functional limitations, balance and kinesiophobia in osteoarthritis and fibromyalgia.

1.1 Introduction

1.1.1 Chronic Pain

Chronic pain is one of the most complex and impactful medical conditions, both at the individual and societal levels[1]. According to the new definition provided by the International Association for the Study of Pain (IASP)[2], it is described as *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"*. Pain is also among the leading reasons individuals seek medical attention, with osteoarthritis (OA), low back pain, and headaches being some of the most frequently reported conditions[1].

Although there is no definitive threshold that separates acute from chronic pain, the latter is generally defined as pain that persists beyond the expected period of tissue healing (typically beyond three months) according to the ICD-11 criteria[3]. Unlike acute pain, chronic pain lacks a clear protective or adaptive function and is increasingly recognized as a disease in its own right. This shift in perspective promotes a management approach focused more on quality of life and functional recovery rather than complete pain elimination[4].

Epidemiologically, chronic pain is not distributed evenly across populations. Data from the Centre for Disease Control indicate higher prevalence rates among women, individuals from lower socioeconomic backgrounds, military veterans, and residents of rural areas[5]. The economic impact is also considerable: in 2010 alone, in the United States, the costs of chronic pain ranged from $560 billion to $635 billion per year, taking into account both direct healthcare costs and lost productivity [6], and these figures are set to rise due to the increase in obesity and sedentary lifestyles.

Biopsychosocial model in chronic pain

Chronic pain is a physiological condition resulting from the complex interaction of biological, psychological and social factors, which determine its onset as well as its chronicity. In this respect, therefore, as with many other conditions, there is increasing talk of an approach based on the biopsychosocial model[7][4].

Depression, anxiety, lack of effective coping strategies and a tendency to catastrophise are some of the psychological elements that favour chronic pain; as well as low level of education, lack of social support and certain cultural norms may also contribute as socio-cultural factors. On the biological level, on the other hand, predisposing elements may include age, gender, genetic alterations, sleep disorders, hormonal imbalances and dysfunction of the endogenous opioid system [8][7][9].

Chronic pain classification

Pain is the result of a complex series of neurophysiological mechanisms involving both the peripheral and central nervous systems[10][11]. These mechanisms can be broadly divided into five main phases[12]:

1. Transduction refers to the process by which nociceptors, specialized sensory receptors located in peripheral tissues, convert noxious stimuli (thermal, mechanical, or chemical) into electrical signals. This is the first step in the pain pathway.

2. Transmission involves the propagation of the electrical signal from the nociceptors through afferent nerve fibers (primarily Aδ and C fibers) to the spinal cord. From there, the signal ascends to the brain via the spinothalamic tract, allowing the central nervous system to process the information.

3. Modulation occurs at both spinal and supraspinal levels. At these points, pain signals can be either amplified or inhibited by a variety of endogenous substances, including endorphins, serotonin, and gamma-aminobutyric acid (GABA). This process can significantly influence how pain is perceived.

4. Perception takes place in the cerebral cortex, where the brain interprets the incoming signals as pain. This stage also involves the integration of emotional and cognitive components, which helps explain why pain is not purely a physical sensation but also has psychological dimensions.

5. Sensitization, both peripheral and central, can develop in pathological conditions. In such cases, nociceptors or central neural pathways become hypersensitive, leading to heightened pain responses and contributing to the development of chronic pain.

These neurophysiological processes underpin the major classification of chronic pain, which is typically divided into three categories: nociceptive, neuropathic, and nociplastic pain[4][10].

Nociceptive Pain

This is the most common type of pain and results from the activation of nociceptive pathways in response to actual or potentially harmful stimuli. It is typical of conditions such as arthritis and spinal pain. Patients often describe it as *"dull"* or *"throbbing."*

- Origin: Activation of nociceptors by real stimuli (e.g., inflammation, trauma, burns).
- Key mechanism: A physiological process involving transduction and transmission in response to tissue damage.
- Examples: osteoarthritis, arthritis, fractures, burns.

Neuropathic Pain

Neuropathic pain arises from damage or disease affecting the somatosensory nervous system. It is characterized by symptoms such as allodynia, paresthesias, and intense paroxysmal pain. Patients often describe it using terms like *"electric"* or *"stabbing."* Compared to nociceptive pain, it tends to cause greater impairment in quality of life.

- Origin: Injury or dysfunction of the peripheral or central nervous system.
- Key mechanism: Aberrant activation of nerve pathways; may involve loss of inhibitory control, increased neuronal excitability, and central sensitization.
- Examples: Diabetic neuropathy, post-herpetic neuralgia, spinal cord injury-related pain.

Nociplastic Pain

Nociplastic pain refers to pain that occurs without clear evidence of tissue damage or nerve injury yet involves abnormal processing of pain signals. It is commonly associated with conditions like fibromyalgia (FM) or irritable bowel syndrome.

- Origin: Pain in the absence of detectable tissue damage or nerve lesions, but with dysfunction in pain modulation.
- Key mechanism: Altered pain transmission and perception; persistent central sensitization and dysregulation of pain circuits.
- Examples: Fibromyalgia, complex regional pain syndrome (CRPS), irritable bowel syndrome.

Mixed Pain

In addition to this classification, a fourth type, so-called mixed pain, has emerged more recently. Indeed, many clinical conditions, such as cancer pain or spinal pain, present overlapping features of several types of pain. These cases, although not yet formally codified in IASP terminology, are increasingly being classified as mixed pain [1][13][14].

For example, the diagnosis of nociplastic pain, which is characteristic of FM, does not require the exclusion of pathophysiological factors such as low-grade inflammation, as in the case of OA, which could be concomitant or act as a trigger factor. In the case of these two specific pathologies, in fact, it was found that FM occurs in comorbidity in up to 25% of patients with OA, thus increasing the mixed pain component[15][16].

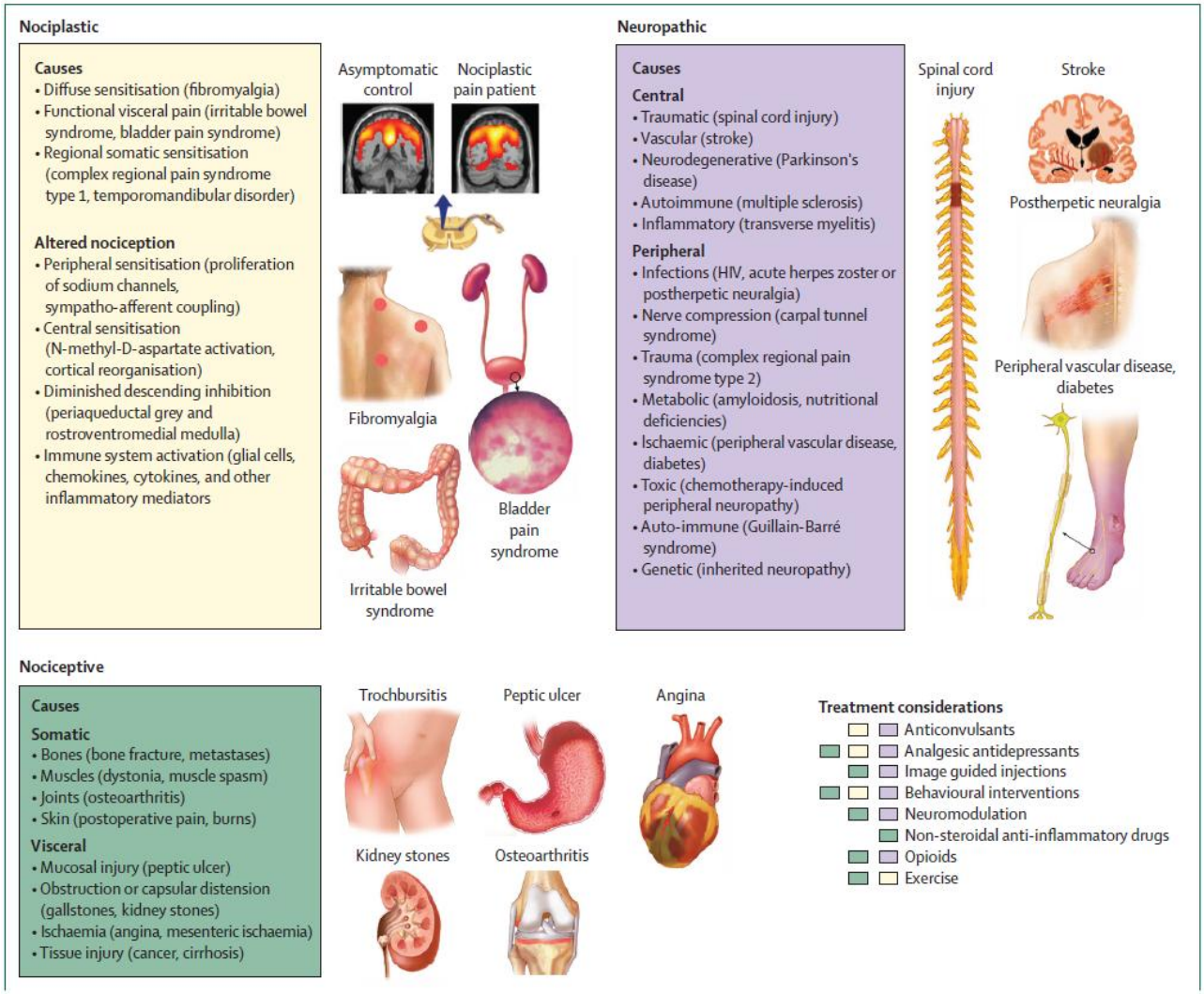

Fig. 1 Illustrative drawing showing the various manifestations of neuropathic, nociceptive, and nociplastic pain, along with treatment considerations. (www.thelancet.com **Vol 397 May 29, 2021)**

Treatment strategies

As previously mentioned, chronic pain has far-reaching implications across all areas of daily life, significantly impacting individuals' quality of life. Functionally, it can interfere with everyday activities to such an extent that it impairs work capacity and, in some cases, may even reduce life expectancy, independent of other risk factors[17][18][19].

Chronic pain compromises functional abilities by limiting autonomy, mobility, and the ability to perform routine tasks. It is also frequently associated with sleep disturbances, anxiety, and depression. These factors often create a vicious cycle in which pain leads to physical inactivity and increased disability.

In theory, optimal pain management should be guided by a clear understanding of the underlying mechanisms. However, in clinical practice, it is not always possible to determine the exact cause of

pain. As a result, treatment is often symptom-based or centred on the specific disease. Clinical guidelines vary depending on the type of pain and the medical discipline involved.

Although pharmacological therapies are often the starting point for pain management, it has been shown that, in terms of cost-benefit ratio, physical exercise may be a better alternative. In a study of Weng et al (2023)[20] authors concluded that physical exercise has effects comparable to those of oral analgesics (NSAIDs and paracetamol) in improving pain and function in patients with knee or hip OA. They also suggested that, given its excellent safety profile, exercise should play a more central role in clinical management, especially in older adults or individuals with comorbidities.

Probably for that reason, among the non-pharmacological treatments, the most effective approach remains a multimodal strategy, combining rehabilitation, psychological support, and behavioural interventions. Self-management is a key component of this approach and may include:

- Weight loss (when appropriate)
- Regular physical activity or exercise
- A balanced diet
- Good sleep hygiene
- Smoking cessation
- Ergonomic modifications

Physical exercise is considered one of the most effective self-management strategies for chronic pain. It can reduce the low-grade inflammatory processes responsible for nociceptive pain, and, more specifically, the appropriate type of exercise can optimize the distribution of mechanical load on joints, thereby reducing mechanical stress and pain, enhancing joint function, and lowering the risk of falls. Moreover, in addition to improving sleep quality and stimulating endorphin release, exercise supports weight management and helps prevent muscle deconditioning.

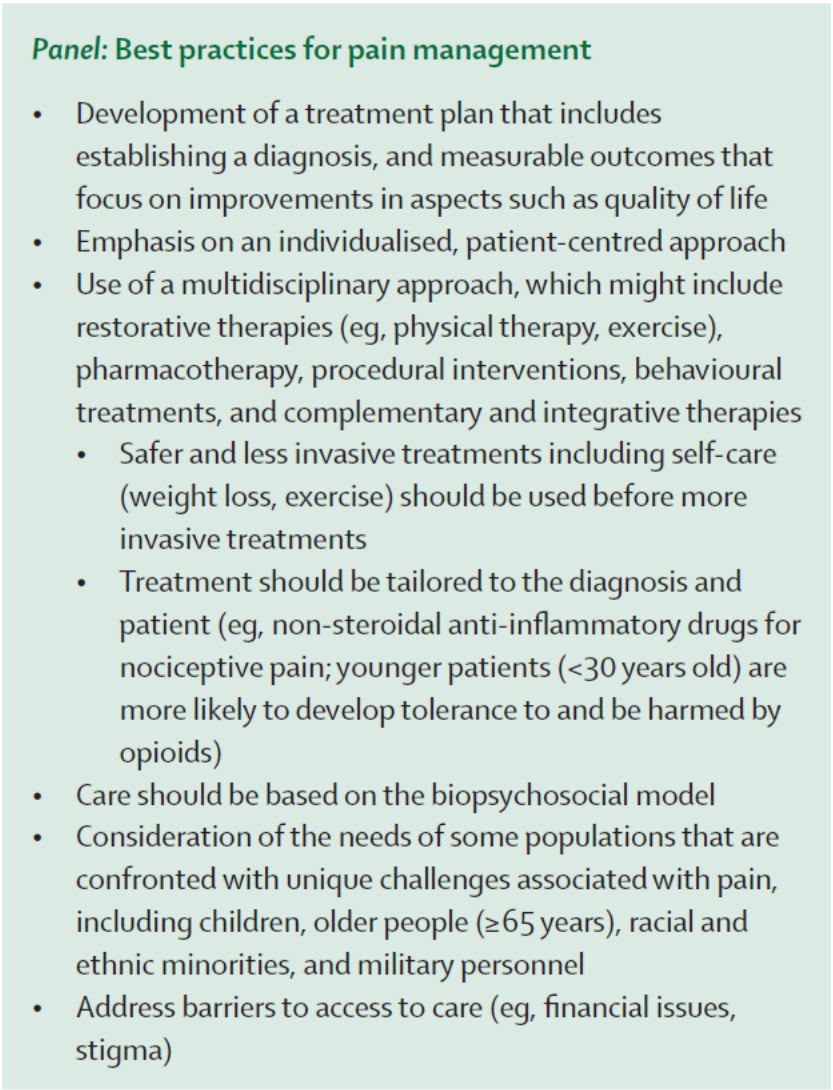

Fig. 2 Best practices guidelines for chronic pain treatment. (www.thelancet.com **Vol 397 May 29, 2021)**

1.1.1.a Chronic Pain in Osteoarthritis and Fibromyalgia

Nowadays, pain in OA is believed to have a multifactorial origin and is increasingly framed through a biopsychosocial model. There is no specific and unambiguous correlation between pain and the diagnostic investigation of the degree of progress of OA, for example through traditional X-ray imaging or MRI. However, it appears that the greater the structural evidence of OA, the greater the frequency and severity of pain. Furthermore, again through diagnostic imaging, it emerges that the presence and severity of pain are associated with specific characteristics of OA, such as changes in synovitis or in the size or number of bone marrow lesions[21].

Pain in OA is also believed to arise from mechanical stress within the joint, which not only causes local nociceptive stimulation but also contributes to accelerating joint degeneration. This mechanical overload leads to microdamage in joint structures, which in turn triggers and sustains inflammatory responses. As a result, increasing attention has been paid to the inflammatory processes that follow mechanical stress, particularly the production of pro-inflammatory mediators within the synovial membrane and cartilage, which play a key role in the perpetuation of pain and disease progression. For that reason, recent advances in the understanding of OA have underscored the significant role of chronic inflammation and immune system dysregulation in the development and maintenance of pain. While OA was traditionally conceptualized as a degenerative "wear-and-tear" condition driven by mechanical joint damage, growing evidence highlights the importance of inflammatory pathways in both joint degradation and pain sensitization.

Specifically, macrophage and T lymphocyte infiltration into the synovial membrane, along with elevated concentrations of pro-inflammatory cytokines and chemokines (e.g., IL-6, IL-1β, IL-8, TNF-α) in synovial fluid and blood, contribute not only to cartilage breakdown, via activation of matrix metalloproteinases, but also to peripheral nociceptor sensitization, thereby amplifying experience of pain[22]. Ongoing research is focused on identifying reliable biomarkers of disease activity and pain in OA. According to Munjal et al. (2019)[23], such markers are detectable in synovial fluid, blood, and urine, each offering specific advantages regarding accessibility and diagnostic value. IL-6, IL-8, IL-10, and TNF-α have emerged as promising indicators, correlating with both pain severity and functional decline[24]. Notably, lifestyle interventions such as moderate physical activity appear to modulate these inflammatory responses: Castrogiovanni et al. (2019)[25] demonstrated in an animal model that regular exercise reduces the expression of IL-1β, IL-6, and TNF-α, while Lee et al. (2011)[26] found elevated levels of IL-6 and TNF-α in OA patients, associated with heightened pain sensitivity.

Nowadays, new insights have transformed our understanding of OA-related pain. Beyond localized nociceptive mechanisms, a subset of patients shows features of central sensitization, whereby the central nervous system amplifies pain signalling independently of peripheral tissue damage[16]. These individuals may present with widespread hyperalgesia, fatigue, sleep disturbances, cognitive dysfunction, and mood disorders, symptoms that closely mirror centralized pain syndromes such as FM.

Therefore, OA is increasingly viewed as a mixed-pain condition [1][11][15], involving both peripheral inflammatory drivers and central nervous system dysregulation. This broader conceptualization has direct clinical implications: while NSAIDs and opioids may alleviate

nociceptive pain, centrally acting medications such as serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine) or anticonvulsants may be necessary to target central pain amplification. Thus, a multimodal and individualized therapeutic approach is essential for optimizing patient outcomes.

Beyond OA, this reconceptualization of chronic OA pain reflects a broader paradigm shift in pain medicine, towards recognizing central nociceptive dysfunction as a legitimate and independent source of pain. While OA involves a combination of nociceptive and nociplastic components, certain conditions, like FM, exemplify a predominantly nociplastic pain phenotype [1].

FM is now widely recognized as the prototypical nociplastic pain condition, characterized by altered central pain processing in the absence of clear peripheral tissue injury or detectable neurological lesions[15]. Unlike nociceptive or neuropathic pain, FM pain arises primarily from dysregulated sensory processing within the central nervous system.

Patients typically experience widespread musculoskeletal pain that is disproportionate to any observable pathology, often accompanied by fatigue, cognitive disturbances ("fibro fog"), sleep disruption, anxiety, and depression. These symptoms are consistent with central sensitization phenomena, including lowered pain thresholds, enhanced temporal summation, and impaired descending inhibitory control.

Importantly, peripheral treatments, such as NSAIDs, opioids, or joint interventions, tend to be ineffective. Instead, effective management requires a comprehensive, personalized strategy aimed at restoring central modulation of pain. This includes pharmacologic treatments like serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine, milnacipran) and certain anticonvulsants (e.g., pregabalin), as well as non-pharmacological interventions such as adapted exercise, cognitive-behavioural therapy, patient education, and sleep hygiene.

This refined understanding underscores the necessity of differentiating nociplastic pain from other pain types in clinical practice to ensure targeted and effective management strategies.

1.1.1.b Functional Limitations in Individuals with Osteoarthritis and Fibromyalgia

Individuals affected by OA and FM experience a wide range of functional limitations that negatively impact autonomy, quality of life, and social participation. These limitations are not solely due to pain but result from a complex interplay of biological, biomechanical, neurophysiological, and psychosocial factors. Functional decline in these chronic conditions is often progressive and

multisystemic, with serious implications including increased fall risk, loss of independence, and heightened disability.

Functional Impairment in Osteoarthritis

In people with OA, progressive joint degeneration and low-grade chronic inflammation lead to a series of functional impairments that compromise mobility, muscle strength, coordination and balance. Structural damage to cartilage and subchondral bone alters joint biomechanics, causing pain, stiffness, and compensatory movement patterns that further accelerate functional decline. Mechanical joint pain and morning stiffness contribute to reduced joint mobility and deterioration of fine motor control [21]. In particular, weakness of the quadriceps and hip stabilizer muscles undermines dynamic stability during ambulation, negatively affecting gait efficiency and increasing fall risk [27].

Several studies have demonstrated that OA, particularly of the hip and knee, is associated with impaired proprioception and altered postural control. Postural sway, the degree of body oscillation while standing, is significantly increased in people with OA compared to healthy controls, indicating challenges in maintaining both static and dynamic balance[28]. This instability is especially pronounced in older adults, in whom OA, sarcopenia, and sedentary behaviour often converge, further reducing functional abilities and therefore independence. These impairments significantly impact quality of life and limit the performance of daily life activities such as walking, climbing stairs, and rising from a chair.

Functional impairment in Fibromyalgia

In FM, functional limitations are often not correlated or disproportionate to objective findings of tissue damages or alterations, yet they are highly disabling. Widespread pain, chronic fatigue, sleep disturbances, and cognitive dysfunction all contribute to reduced general fitness and diminished functional abilities[29]. From a neurophysiological perspective, individuals with FM show disrupted transmission and processing of nociceptive and somatosensory inputs, which distorts movement perception and physical effort tolerance[15].

Evidence also shows that individuals with FM experience balance impairments even in the absence of observable peripheral lesions. Postural sway is significantly greater, particularly under altered sensory conditions such as eyes-closed or unstable surfaces [30]. Increased sway variability and asymmetrical motor patterns further indicate impaired neuromuscular coordination. This postural instability contributes to a persistent sense of movement insecurity, which can worsen anxiety and

reinforce avoidance behaviours, and can explain higher levels of kinesiophobia compared to healthy subjects[31].

The Role of Kinesiophobia

A key factor that exacerbates functional limitations in both OA and FM is kinesiophobia: a persistent, irrational fear of movement stemming from the belief that physical activity will worsen pain or cause further injury[32]. This fear, often exacerbated by previous episodes of acute pain or failed treatment attempts, leads to the adoption of avoidance behaviours, such as limiting movement or physical inactivity[33]. This, in turn, initiates a vicious cycle: inactivity leads to deconditioning, joint stiffness, postural dysfunction, and heightened pain perception[32].

Kinesiophobia has been identified as a significant predictor of disability in chronic musculoskeletal pain conditions. In individuals with knee OA, high fear-of-movement scores are associated with poorer function on WOMAC, LEFS and Knee Outcome Survey-Activity of Daily Living Scale questionnaires[34]. Similarly, in people with FM, kinesiophobia creates a vicious cycle linked to greater disability, increased pain intensity and reduced adherence to exercise interventions[35].

Clinical Implications

Functional limitations in OA and FM do not stem solely from peripheral tissue damage or central sensitization, but also from functional, behavioural and cognitive factors. Therefore, clinical assessment should include both objective measurements of mobility, strength, and balance, as well as psychometric tools to detect kinesiophobia and other psychosocial barriers to recovery.

Addressing these factors in clinical practice enables the development of more effective and individualized rehabilitation programs. In particular, activity-based interventions are among the most suitable and effective approaches, as they can operate on multiple levels: not only restoring physical capacity, but also reducing fear, rebuilding confidence in movement, and enhancing patients' sense of autonomy and independence.

1.2 Physical activity for treating chronic pain and improving functional abilities

The recognition of chronic pain as a disease entity in its own right has made a biopsychosocial approach to treatment essential, one that is grounded in a multimodal and individualized therapeutic plan [1]. This may encompass pharmacological interventions (primarily non-opioid medications such as NSAIDs, antidepressants, and anticonvulsants), invasive procedures (e.g., neuromodulation),

nutritional strategies aimed at weight management and the reduction of low-grade systemic inflammation, psychological support, physiotherapeutic techniques, meditation, and acupuncture [1].

Tailored physical exercise is now widely regarded as a first-line therapeutic tool, particularly effective in managing nociceptive and nociplastic pain. It plays a crucial role not only in enhancing physical function and mitigating central sensitization, but also in preserving or improving body composition parameters, fostering metabolic health, and promoting overall psychosocial well-being[11][15].

Supporting this, a Cochrane overview synthesized data from 21 systematic reviews comprising 381 studies and over 37,000 participants affected by various chronic pain conditions, including low back pain, FM, OA, and cervical disorders. The interventions assessed included aerobic, strength, flexibility, balance, and core stability exercises, as well as yoga, Pilates, and tai chi [36].

The main findings indicated improvements in physical function, statistically significant and of small-to-moderate effect size. Pain severity also tended to decrease following exercise interventions, although results were not universally consistent, with some studies reporting no significant differences. Quality of life and psychological well-being showed favourable changes in several reviews.

Importantly, physical activity was not associated with serious adverse events. Mild and transient musculoskeletal soreness was the most commonly reported side effect. However, the overall quality of the evidence was rated as low, primarily due to small sample sizes, limited duration of follow-up (typically less than six months), and methodological heterogeneity. These limitations are common in exercise science research, particularly in clinical settings.

Nevertheless, the authors concluded that physical activity remains a safe and potentially effective therapeutic option that should be integrated into chronic pain management programs.

Beyond its impact on pain modulation and functional capacity, physical activity is also instrumental in managing parameters of body composition, such as reducing fat mass, preserving or increasing lean mass, and counteracting sarcopenia, particularly in older adults or those with sedentary lifestyles. These physiological adaptations contribute significantly to improved metabolic health, greater independence, better quality of life, prevention of new non-communicable diseases and a reduced risk of falls.

Physical activity also plays a central role in improving the overall health of individuals suffering from chronic pain or from conditions in which chronic pain is a prominent feature. As previously mentioned, such conditions are often associated with a decline in functional abilities, which in turn negatively affects quality of life and personal autonomy.

Through tailored exercise programs, it is possible not only to counteract further functional decline caused by specific clinical conditions or by the natural aging process, but also to prevent the onset of comorbidities associated with a sedentary lifestyle.

An equally critical benefit of adapted physical exercise lies in reducing kinesiophobia, an often overlooked but central factor in the perpetuation of chronic pain syndromes. Fear of movement leads to avoidance behaviours, which in turn reinforce physical deconditioning, increased pain perception, and loss of autonomy. Breaking this cycle through gradual, guided, and empowering movement-based interventions is essential for restoring confidence in physical ability and regaining functional independence.

Although physical activity and exercise are now recognized as true non-pharmacological therapies for nearly all chronic non-communicable diseases, these terms encompass a wide range of approaches that inevitably lead to different outcomes. When referring to physical exercise, it is possible to encounter intervention protocols based on resistance training, aerobic training, combined modalities, or neuromuscular training, each of which includes numerous subcategories.

In this context, identifying the most appropriate type of activity, in terms of method, duration, volume, workload, intensity, and progression, becomes a key objective in designing targeted interventions.

Moreover, interest has been growing in exercise practices that align with a biopsychosocial model, embracing a holistic approach aimed at the overall care of the individual. Within this framework are well-known and widely studied activities such as yoga, tai chi, and Pilates, as well as, more recently, the Gyrokinesis® method. These practices, due to their highly proprioceptive and coordinative movement patterns, can be classified as neuromuscular activities, and more specifically, as sensorimotor exercises.

These types of practices will be examined in greater detail over the course of this thesis.

1.3 Rationale and specific aims of the experimental chapters

Adapted physical exercise is now widely recognized as a key component in the non-pharmacological therapeutic management of chronic pain, functional limitations and kinesiophobia, particularly in rheumatic diseases affecting the musculoskeletal system. Sensorimotor training, considered a subcategory of neuromuscular training, remains one of the least studied types of exercise in this population, despite its features suggesting it could be the most appropriate and effective initial approach.

In conditions such as OA and FM, though through different mechanisms, this type of training appears to yield significant benefits. These include not only pain reduction and improvements in functional capacity and quality of life, but also the ability to overcome typical barriers to physical activity in these individuals, such as kinesiophobia.

Moreover, sensorimotor training is a defining component of several exercise modalities grounded in biopsychosocial and multimodal approaches, aiming to treat the individual through a holistic perspective. Among these, the most well-known and widely studied are yoga, tai chi, and Pilates. However, the Gyrokinesis® method is also gaining popularity. Although still underexplored in the literature, it already shows strong potential in the field of adapted physical exercise.

From this background, the following research questions emerged, which form the foundation of the studies presented in Chapters 2, 3, 4 and 5:

Chapter 2: *"Role of exercise on pain, functional capacity, and inflammatory biomarkers in osteoarthritis: systematic review and meta-analysis"*

- Research question: Among different exercise modalities, which are most effective in managing pain, enhancing physical function, and modulating inflammatory markers in people with osteoarthritis?

ABSTRACT: Osteoarthritis is a complex disease that causes pain, stiffness, swelling, limiting function and mobility, thus interfering with daily life, and affecting persons' personal, social, and psychological aspects. To evidence the role of exercise on pain reduction and the effectiveness of one type of training over another in terms of pain, functional capacity, and inflammatory biomarkers in OA.

Studies retrieved from Web of Science, PubMed and Scopus databases were systematically reviewed. RCTs involving physical exercise interventions in participants with OA were included. The three main outcomes considered in the systematic review were pain, functional capacity and inflammatory biomarkers. The effects of different type of interventions (aerobic, resistance, combined, neuromuscular and others) were analysed based for each outcome. Systematic review and meta-analysis were conducted follow the PRISMA Statement.

21 studies were included in the systematic review and 11 in the meta-analysis. The meta-analysis was conducted on pain in training intervention subgroups, showing a larger effect size for neuromuscular training -2,26 (95% CI: -4,37; -0,14). Functional capacity and inflammatory biomarkers were analysed only with a systematic review because it was not possible to estimate the efficacy of the different training protocols with a meta-analysis.

Neuromuscular training protocols seem to be the most effective in reducing pain in OA. Direct comparison of different training treatment options on functional capacity and inflammatory biomarkers for OA is not currently feasible in practice, due to the heterogeneity of the test and the small number of studies. High-quality physical exercise interventions studies are warranted to estimate their effectiveness more accurately on pain, functional capacity, and inflammatory status in OA.

Chapter 3: *"Sensorimotor training in Osteoarthritis: effects of 24-weeks GYROKINESIS method® and Pilates on balance control, functional abilities and pain"*

- Research question: Does a 24-week Gyrokinesis® program improve balance, pain, kinesiophobia, and physical function in individuals with osteoarthritis (OA), and are these effects comparable to those achieved with a standard care intervention such as Pilates?

ABSTRACT: Osteoarthritis (OA) is a prevalent degenerative joint disease often leading to impaired postural control, pain, and reduced physical function. Exercise is considered a first-line treatment, with sensorimotor approaches showing promising results. While Pilates is a well-established sensorimotor method, evidence on the Gyrokinesis method (GK) in OA populations is scarce.

To compare the effects of a 24-week Gyrokinesis method versus Pilates intervention on balance control, functional abilities, pain and kinesiophobia in women with knee OA.

Twenty women (aged 60 ± 7 years) with grade 2 or 3 knee OA were assigned to either GK (n=12) or Pilates (PL, n=8). Both groups trained twice weekly for 24 weeks. Pre- and post-intervention assessments included postural sway parameters (RMS, velocity, frequency), physical function tests (e.g., TUG, Sit-to-Stand), flexibility, pain (Brief Pain Inventory), kinesiophobia (Tampa Scale), and quality of life (SF-36).

GK resulted in significantly greater improvements than PL in postural sway measures (mean velocity in both legs), physical function (TUG, Sit-to-Stand, Step test), and pain reduction ($p<0.05$). Both groups improved shoulder mobility. No significant between-group differences were observed for kinesiophobia or SF-36 scores.

Gyrokinesis method may be more effective than Pilates in enhancing balance, reducing pain, and improving physical function in women with knee OA. These findings support the integration of Gyrokinesis method into rehabilitation programs for OA, though further randomized trials are warranted.

Chapter 4: this chapter presents the results of an exploratory study titled “Movement Quality Matters: Divergent Inflammatory and Antioxidant Responses to Two Sensorimotor Exercise Interventions in Osteoarthritis” on the effects of sensorimotor training on inflammatory biomarkers and oxidative stress parameters.

- Research question: Can 24-week Gyrokinesis® and Pilates interventions modulate specific inflammatory (TNF-α, IL-1 beta) and oxidative stress (tGSH, GSSG, GSH/GSSG, CK, LDH) biomarkers in individuals with osteoarthritis?

ABSTRACT: This exploratory analysis aimed to investigate preliminary changes in inflammatory and oxidative stress biomarkers following two 24-week sensorimotor exercise interventions, Gyrokinesis® (GK) and Pilates (PL), in individuals with osteoarthritis (OA). A total of 17 participants (GK= 9; PL= 8) underwent blood sampling before and after training to assess IL-1β, TNF-α, total and oxidised glutathione (tGSH, GSSG), the GSH/GSSG ratio, and cellular damage markers (lactate dehydrogenase LDH, creatine kinase CK).

Both groups showed significant within-group increases in IL-1β and TNF-α concentrations after the intervention, with no statistically significant between-group differences. tGSH increased in GK group and decreased in PL group, suggesting possible differences in antioxidant responses. No significant variations were observed for GSSG, LDH, or CK, although a slight decrease in LDH was noted in GK group. Exploratory correlation analyses revealed opposite, non-significant trends between changes in pain perception and tGSH levels in the two groups.

Overall, these preliminary findings indicate that sensorimotor exercise may influence inflammatory and redox parameters in OA, although the direction and magnitude of these effects appear to differ depending on the exercise modality. Given the limited sample size, the results should be interpreted with caution. Further studies with larger cohorts are warranted to confirm these observations and to clarify the potential links between movement quality, oxidative stress, and pain modulation in osteoarthritis.

Chapter 5: *“Feasibility and Preliminary Effects of a 12-Week Sensorimotor Training Program in Fibromyalgia: A Proof-of-Concept Pilot Study”*

- Research question: What are the effects of a 12-week sensorimotor training program on pain, functional fitness, and psychological factors such as sleep quality, quality of life, and kinesiophobia in individuals with fibromyalgia?

ABSTRACT: Fibromyalgia (FM) is a complex, multifactorial condition characterized by chronic widespread pain, fatigue, and other somatic and psychological symptoms. While exercise is the only

strongly recommended intervention by current EULAR guidelines, research on body awareness and motor control-oriented modalities remain limited. This pilot study assessed the feasibility and preliminary effects of a 12-week sensorimotor training program on pain, symptoms, sleep quality, psychological aspects, and physical function in individuals with FM.

Five participants with FM (mean age 56 ± 7.7 years) completed a 12-week supervised sensorimotor training program (2 sessions/week). Assessments were conducted pre- and post-intervention using validated questionnaires (BPI, FIQR, PSQI, SF-36, TSK) and physical tests (Sit-to-Stand, flexibility, balance). Due to the small sample, non-parametric analyses were used.

The intervention was feasible, with full adherence, no drop out and no adverse events. Significant improvements were observed in perceived pain (BPI, $p=0.043$, $g = -2.14$), FIQR total and function domain scores ($p=0.043$, $g=-1.26$), and sleep quality (PSQI, $p=0.042$, $g=-1.42$). Physical function improved significantly in Sit-to-Stand, Sit and Reach, Trunk Rotation, and static/dynamic balance tests ($p<0.05$), with moderate-large effect size. No significant changes were found in quality of life and kinesiophobia.

Sensorimotor training is a feasible and potentially effective intervention for fibromyalgia symptoms, with preliminary benefits on pain, sleep, disease symptoms and physical function. These findings support further investigation in larger randomized controlled trials to establish its clinical utility and long-term outcomes.

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CHAPTER 2

First study

“Role of exercise on pain, functional capacity, and inflammatory biomarkers in osteoarthritis: systematic review and meta-analysis”

Published as:

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PROSPERO registration number: CRD42023481061

Abbreviations:

1RM 1 Repetition maximum

30” STS 30” Sit to Stand

6MWT 6 Minutes Walking test

AROM Active knee flex/extension

CI confidence interval

COMP cartilage oligomeric matrix protein

CRP C-reactive protein

CTX-II C-terminal cross-linked telopeptide of type II collagen

ES effect size

IL interleukin

KOOS Knee Osteoarthritis Outcome Scale

MMP matrix metalloproteinase

NRS Numeric Rating Scale

NSAIDs non-steroidal anti-inflammatory drugs

OA osteoarthritis

PA physical activity

PE physical exercise

PT peak torque

PTBW peak torque/body weight

QoL quality of life

RCT randomize control trial

ROM Range of Motion

RSTN resistin

SE standard error

SPPB Short Physical Performance Battery

sTNFR tumor necrosis factor receptor

TNF- α tumor necrosis factor alpha

TST Time Stands

TUG Time Up and Go

VAS Visual Analogue Scale

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

YLDs years lived with disabilities

2.1 Introduction

Osteoarthritis (OA) is an active dynamic alteration with a complex and unclear pathogenesis, in which mechanical and inflammatory factors gradually lead to structural changes of the entire joint [1-3].

In 2020, OA affected 8 % of the world's population, which is 595 million people, with an increase of 132 % in the last 30 years [4]. In addition, due to the increasing average age of the world population and obesity incidence, the OA new diagnosis will tend to increase over the years [5-7]. Osteoarthritis mainly affects the knee, but several joint can be involved, such as hip and hand [4].

In 2019, OA was the 15th highest cause of years lived with disabilities (YLDs) worldwide and was responsible for 2% of the total global YLDs [5,6,8]. All-age YLDs rates increased by 69% for hand osteoarthritis, 57% for knee osteoarthritis, and 56% for hip osteoarthritis [4]. This condition leads to an enormous cost for national healthcare systems, and in five European countries (France, Germany, Italy, Spain, UK) it has been estimated that the annual direct cost for OA is up to € 7.2 billion, and the indirect cost is up to € 4.6 billion [9,10].

As reported by persons [11], OA causes pain, stiffness, and swelling, limiting function and mobility, thus interfering with daily life, and affecting their personal, social, and psychological aspects. Pain is the most disabling symptom, with the greatest negative impact on daily life, and its relief should be the first goal of treatment. In addition, most people with OA, especially after the age of 65, may suffer from various comorbidities due to the sedentary lifestyle induced by pain [12].

Pain seems to have a multifactorial origin and is increasingly framed through a biopsychosocial model [8]. In fact, there is no specific and unambiguous correlation between pain and the diagnostic investigation of the degree of progress of OA, and it is possible to find people with evident radiological signs of OA but who report no pain. Both peripheral, such as increase in nociception due to joint degradation, and central factors, such as central sensitisation, converge in this pain mechanism of OA. The central pain sensitisation, defined as an amplification of neural signalling within the central nervous system that elicits pain hypersensitivity, could represent a reason for this discrepancy between pain and radiographic severity in OA, because markers of central sensitisation are strongest among people with high pain in the absence of moderate-to-severe radiographic OA [13]. Indeed, the greater the structural evidence of OA, the greater the frequency and severity of pain [1]. Furthermore, recent evidence has shown that chronic inflammation of affected joints can influence pain, and

immunological-inflammatory processes seem to play a decisive role in the pathogenesis of OA [3]. From a peripheral point of view, nociception of this disease is mainly determined by the imbalance between proinflammatory and anti-inflammatory mediators, such as interleukins and cytokines (e.g. interleukins (IL) 6, 1β, 8, 10, tumor necrosis factor (TNF)- α) with a consequent increase in matrix metalloproteinases, which leads to low-grade inflammation, responsible for the systemic degradation of the entire structure, and thus also causes an increase in the peripheral sensitisation of the free endings in the joint, increasing the pain symptoms[14]. Therefore, the concept of nociplastic pain is also being introduced for this pathology, possibly due to an alteration of nociception and central sensitisation as the basic mechanism [13], but on this the debate is still open.

Treatments in OA mainly focus on improving quality of life (QoL), reducing pain, and increasing functional capacity without enhancing diseases' adverse effects, as there is still no cure for this condition [8,15]. Pharmacological treatment, such as the use of non-steroidal anti-inflammatory drugs or paracetamol, is widely used but given the possible adverse effects and unfavourable cost-benefit ratio, national health and research authorities indicate physical activity (PA) and physical exercise (PE) as important treatments for OA[16-19]PA consists in any bodily movement produced by skeletal muscles that result in energy expenditure, while PE, which is a subcategory of PA, is intended as a planned, structured, repetitive, and purposive activity so that the improvement or maintenance of one or more functional parameters can be objectively quantified. PA can be extremely effective in reducing chronic non-specific or OA-induced pain, as well as physical and psychological function and QoL [20] and in the guidelines [8,16] for OA exercise is always mentioned as a focal point. Even PE such as, land-based [20] or water-based exercises [21], as well as aerobic and Pilates [22], specific strengthening [23], or neuromuscular [24] exercises have proven effective in reducing OA symptoms and improving participants' QoL and general health. Moreover, in a recent, preliminary analysis of the comparative effectiveness on pain and functional abilities between PA and the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol for knee or hip OA, it was found that PA has similar effects to conventional therapies and at the same time it has no side effects [15,25]. In fact, no serious adverse reactions or aggravation of pre-existing symptoms after training have been reported [20]. These data are in line with a previous study by Bloch et al 2022[26], in which the authors compared the effectiveness of opioids, NSAIDs and exercise therapy for OA pain of the knee. In addition, one of the potential effects of PA, is the anti-inflammatory mechanisms induced by the muscle contraction [24]. In this way, it is possible to counteract low-grade inflammation, that plays a crucial role in the pathogenesis and progression of OA and is also associated with comorbidities that may be concomitant to OA, such as cardiovascular disease, type II diabetes or dementia, feeding a vicious circle [27].

To date studies evidenced that even a slight increase in daily PA is effective in improving the symptoms of OA[28], moreover it seems that PE aimed at increasing strength, flexibility and aerobic capacity may be the most effective in the management of OA of the lower limbs, which is the most studied site[29], and should be supervised and performed three times a week[30].

Nevertheless, new experimental studies have been conducted in recent years, more specific in terms of investigation of perceived pain, analysis of functional parameters, and inflammatory biomarkers, but clear indications on the type, time, and load of exercise in participants with OA are still lacking. Therefore, this review, aims to identify which type of exercise is the most effective in reducing pain, while also considering the effects on functional capacity and inflammatory processes in people with OA. The research is focused on the latest articles, published in the past 14 years, in order to evidence the newest results about this topic.

2.2 Methods

2.2.1 Search Strategy and Selection Criteria

This systematic review was performed in accordance with the PRISMA 2020 guidelines [31].

Studies with interventions based on exercise were considered for inclusion. Resistance, aerobic, neuromuscular, or combined/multimodal protocols were considered as 'exercise interventions'. Exercise training such as Tai-chi, Pilates, Yoga, stretching or techniques that could be defined as neuromuscular or sensorimotor activities, were included in the group of neuromuscular training due to their proprioceptive and stabilising component. Only supervised interventions were considered for inclusion. While multidisciplinary program including education/psychological intervention/manual therapy and physiotherapy treatment were excluded. Although research initially included participants diagnosed with OA at multiple sites, the included studies all focused on knee osteoarthritis. The primary outcome was pain intensity, while secondary outcomes were either the analysis of functional assessments, or the analysis of inflammatory biomarkers related to OA, or both simultaneously. Only randomised control trials (RCTs) were considered eligible, on the contrary reviews, meta-analyses, and case reports were excluded. Studies that did not report intervention protocols in a clear and detailed manner were excluded. All details of the screening are given in the flow chart in Fig1.

The following databases were used for the systematic search of the relevant literature: PubMed, Web of Science, Scopus; examining studies published between 2010 and 2024. The last consultation of the databases took place on 16th April 2024. Rayyan [32] web application was used for the electronic management of the literature. Publications before and after these dates have not been considered. The

following search terms were used: ("chronic pain" OR "pain" OR "Chronic musculoskeletal pain") AND (“Physical activity” OR “Muscle contraction” OR “Exercise” OR “Physical exercise” OR “Exercise therapy” OR “Resistance training” OR “Walking” OR “Circuit-based training” OR “Strength training” OR “Weight-bearing exercise” OR “Aerobic training” OR “Cardiorespiratory training” OR “Fitness” OR “Endurance training” OR “Exercise prescription” OR “Muscle strength” OR “Balance training” OR “Sensorimotor training”) AND (“Osteoarthrosis” OR “Osteoarthritis”) AND (“functional parameters” OR “functional assessments” OR “functional abilities” OR “functional capacities”) AND (“Inflammation” OR “Biomarkers” OR “Clinical outcome” OR “Inflammatory biomarkers” OR “Interleukins” OR “Cytokines”).

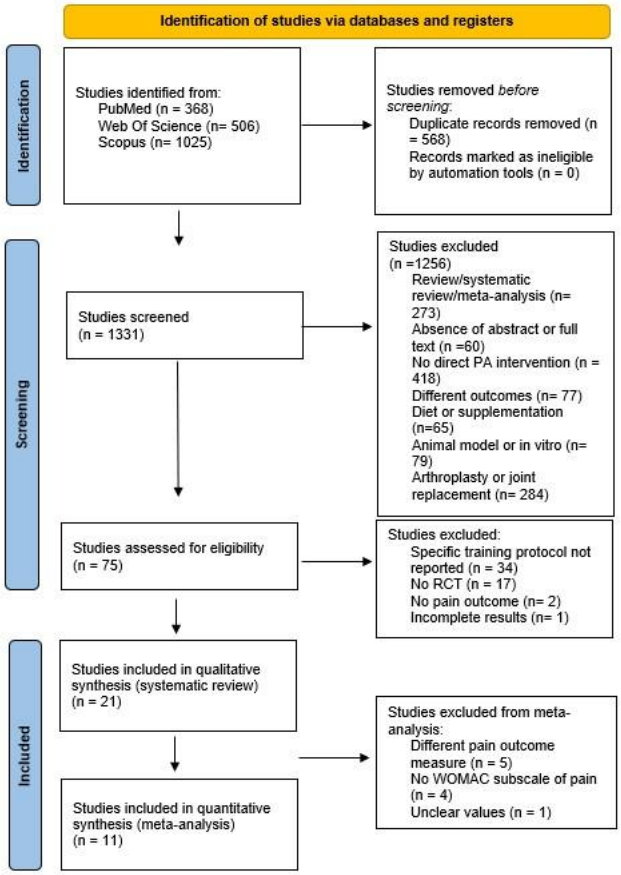

Fig.1 PRISMA 2020 flow diagram of study selection

2.2.2 Study Selection, Data Collection and Quality Assessment

The full text of eligible articles was read by two different authors (C. M. and E. G.) and the following data were extracted: author(s), year of publication, study design, sample size, inclusion and exclusion criteria, intervention type, description of the intervention, outcomes regarding pain, functional assessments, and biomarkers.

Internal validity was assessed using the Risk of Bias Tool I [33]. Each study was then assessed based on the 7 domains for risk of bias: (1) random sequence generation, (2) allocation sequence concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. Studies were classified as “Low”, “High”, “Unclear” and “Not applicable” risk of bias. Considering the difficulty to blind participants to group assignment in exercise intervention protocols, some studies that presented high risks of bias in the 3rd and 4th domains were nevertheless considered to be of a low overall risk of bias. The results of the risk of bias analysis are shown in the Fig 2.

Fig. 2 Risk of bias with traffic lights plot of the included studies.

2.2.3 Data Synthesis and Statistical Analysis

All analyses were conducted by IBM-SPSS-ver.29. The effect size (ES), the associated standard error (SE) and 95% confidence interval (CI) for each study were calculated using Cohen’s d. ES were calculated so that reductions in pain resulted in negative ESs. The pooled, sample-weighted, average

ES were computed using a random effects model. ES was interpreted following on the Cohen rules: < 0.2 (none), 0.2 to 0.5 (small), 0.5 to 0.8 (moderate), and > 0.80 (large). To determine heterogeneity the I2 statistic was applied. I2 was interpreted as follow I2 < 25% (low), 25 to 75% (medium), and > 75% (high) indicate different levels of heterogeneity. Publication bias was assessed via visual inspection of a funnel plot and Egger's test.

2.3 Results

This review identified 1899 articles (Fig 1). After removing duplicates, the remaining 1331 articles were screened for eligibility based on the title and Abstract. As reported in the Fig. 1, studies were excluded when they were identified as reviews, meta-analyses, case study or non-RCTs and due to the absence of the full text and of a direct exercise intervention. For the remaining studies, the exclusion criteria were: different outcomes, use of diet and/or supplementation, studies on animals or in vitro, and studies on arthroplasty or joint replacement.

This process resulted in the inclusion of 21 studies for the systematic review and 11 for the meta-analysis.

2.3.1 Study population

The total study sample consisted of 1461 participant (Tab. 1), aged between 38 and 85. While 3 studies included only women [34-36], in the others both men and women were enrolled. Although the search criteria included many body sites, in the end, only studies on the knee were included, which are more present in the literature.

2.3.2 Characteristics of the included studies

In this review were included RCTs studies only, and all the characteristics are reported in table 1. Due to the inclusion criteria, a total of 21 studies were found in the literature that analyse the effect of specific training on pain and functional assessment or pain and inflammatory biomarkers or studies that include all these three outcomes. Among these studies, 3 analysed only pain [37-39], 11 pain and functional assessments [34, 40-49], 3 pain and inflammatory biomarkers [35,50,51], and 4 pain, functional assessments and inflammatory biomarkers [36, 52-54].

Studies comparing more than one type of exercise, either in comparison or versus a control group without intervention, were divided to better answer the research question and to compare different types of exercise. Across all studies, resistance training (n= 19) and multimodal/combined training (n= 13), were the most reported exercise modality, followed by neuromuscular (n= 2), Qigong or Yoga (n= 3), aerobic (n= 1), active video game (n= 1), and stretching (n= 1). Moreover, 2 study used the addition of vibratory platform in combination with resistance training [52,54], 1 the addition of

blood flow restriction in combination with resistance training[34], 1 the application of kinesio-tape during a combined training protocol[35], 1 the use of photobiomodulation during a multimodal/combined training protocol, 1 the electrical muscle stimulation during resistance exercise[36], and 1 the use of low-level-laser therapy plus strength training[47]. Interventions ranged from 4 to 24 weeks in duration (3 interventions of 4 weeks; 6 of 6 weeks; 8 of 8 weeks; 16 of 12 weeks; 2 of 16 weeks; 5 of 24 weeks).

Table 1. General characteristics of included studies.

References	Tot Sample Size	Study Population	Type of exercise	Intervention	Duration	Outcome	Results
Simão et al (2012) [52]	n = 35	Age 40 – 70 years Knee OA	Resistance	Group 1 = Squat exercises Group 2 = Squat exercises on a vibratory platform CG = no exercise	3 times weekly for 12 weeks	Pain Functional assessment Biomarkers	Group 1: ↓ WOMAC, sTNFR2 ↑ sTNFR1, 6-MWT, Berg Balance scale Group 2: ↓ WOMAC, sTNFR1, sTNFR2, ↑ 6-MWT, Berg Balance scale CG: ↑ sTNFR1, sTNFR2
Knoop et al (2013) [40]	n = 159	Age 40 – 75 years Knee OA	Combined/multimodal	IG= Combined/multimodal + specific knee joint stabilization training CG= Combined/multimodal	7 times weekly for 12 weeks (2 structured; 5 home based)	Pain Functional assessment	IG: ↓ WOMAC, NRS, TUG ↑ isokinetic strength CG: ↓ WOMA

							C, NRS, TUG ↑ isokinetic strength
Bennell et al (2014) [41]	n = 100	Age ≥ 50 years Knee OA	Neuromuscular Resistance	NEXA= 62 sessions of neuromuscular exercises QS= 62 sessions of quadriceps strengthening exercises	12 weeks: 14 sessions supervised; 48 sessions home-based	Pain Functional assessment	NEXA: ↓ VAS, WOMAC, 30, 4 square step test ↑ lower limb isometric strength, 30’ STS, step test, single leg stance QS: ↓ VAS, WOMAC, stair climb, 4 square step test, single leg stance ↑ lower limb isometric strength, 30’ STS, step test
Samut et al (2015) [53]	n = 42	Age ≥ 50 years Knee OA	Resistance Aerobic	Group I = Isokinetic protocol: 6 sets of concentric flexion and extension at angular velocities of 60º /s, 90º /s, 120º /s and 180º /s Group II = *Aerobic training* 65 %-75% of age-related heart rate Group III = no exercise	3 times weekly for 6 weeks	Pain Functional assessment Biomarkers	Group I: ↓ VAS, WOMAC, CRP, TNF-α ↑ 6-MWT, 30’ STS, IL-6 Group II: ↓ VAS, WOMAC, CRP, IL-6, TNF-α ↑ 6-MWT, 30’ STS

							Group III: ↑ 6-MWT, 30’ STS, IL-6 ↓ CRP, IL-6
Wang et al (2016) [54]	n = 99	Age 40 - 65 years Knee OA	Resistance	IG = Whole body vibration + Quadriceps strengthening exercises protocol CG = Quadriceps strengthening exercises protocol	5 times weekly for 24 weeks	Pain Functional assessment Biomarkers	IG: ↓ VAS, WOMAC, TUG, serum COMP, urinary CTX-II ↑ 6-MWT, ROM, knee flex/ext strength, active knee flx/ext CG: ↓ VAS, WOMAC, TUG, serum COMP, urinary CTX-II ↑ 6-MWT, ROM, knee flex/ext strength, active knee flx/ext
Cheung et al (2016) [42]	n = 83	Age >60 years Knee OA	Neuromuscular/Yoga Combined	HY = yoga training protocol ASE = 15 min mild aerobic exercise + 30 min of strengthening exercises CG = education brochures	1 time weekly for 8 weeks supervised + 30 min 4 times weekly home-based	Pain Functional assessment	HY: ↓ WOMAC, HADS ↑ SPPB, SF-12 ASE: ↓ WOMAC, HADS ↑ SPPB, SF-12 CG: no changes
Zakir et al (2016)	n = 60	Age 40 - 60 years	Manual therapy	MT = Long axis traction technique,	3 times weekly	Pain	MT = ↓ WOMA

[39]		Knee OA	Combined	Maitland mobilizations COMB = stretching and strengthening exercises program	for 4 weeks (30 mins per session)	Self-reported physical function	C COMB = ↓ WOMAC
Branco Ferraz et al (2018) [34]	n = 48	Age 50 – 65 years Women Knee OA	Resistance	BFRT= Blood-flow restriction + Low-intensity resistance training 30% of 1RM HI-RT= High-intensity resistance training – 80% of 1RM LI-RT= Low-intensity resistance training – 30% of 1RM	2 times weekly for 12 weeks	Pain Functional assessment	BFRT: ↓ WOMAC, TUG ↑ 1 RM, TST HI-RT: ↓ WOMAC, TUG ↑ 1 RM, TST LI-RT: ↓ WOMAC ↑ 1 RM, TST
Hernandez et al (2019) [43]	n = 47	Age >40 years Knee OA	Combined/Multimodal	IG: combined + core stability training CG: combined training	3 times weekly for 12 weeks	Pain Functional assessment	IG: ↓ VAS, TUG, WOMAC, ↑ Step Test; no changes in 6MWT CG: ↓ VAS, TUG, WOMAC, ↑ Step Test; no changes in 6MWT
Vincent et al (2019) [44]	n = 54	Age 60-85 years Knee OA	Resistance	ECC RT: lower limb eccentric exercise CNC RT: lower limb concentric exercise CG: no exercise	2 times weekly for 16 weeks	Pain Functional assessment	ECC RT: ↑ 1RM (leg curl, leg extension, leg press), ↓ WOMAC CNC RT: ↑ 1RM (leg curl, leg extension, leg press), ↓ WOMAC

							CG: no changes
Lin et al (2020) [45]	n = 80	Age 40 – 85 years Knee OA	Active video game Combined/multimodal	AVGs: *Active Video Games:* 20 min of active video games (2 sessions: Whack-a-mole, Archery) TE: 20 min of therapeutic exercise	3 times weekly for 4 weeks	Pain Functional assessment	AVGs: ↓ WOMAC, 10-m walking time, stairs ascent time ↑ dynamic balance TE: ↓ WOMAC, 10-m walking time, stairs ascent time ↑ dynamic balance
Holm et al (2020) [46]	n = 90	Age 52-76 years Knee OA	Combined Neuromuscular	IG: Strength - Neuromuscular – Education Protocol CG: NEMEX – EDU protocol	2 times weekly for 12 weeks	Pain Functional assessment	IG: ↑ KOOS ↓ 40 m walk test, stair climb test CG: ↑ KOOS ↓ 40 m walk test, stair climb test
Oğuz et al (2021) [35]	n = 22	Age 38 - 60 years Women Knee OA	Combined/multimodal	ET + KT = combined training protocol plus knee kinesio tape application ET = combined training protocol	3 times weekly for 6 weeks	Pain Biomarkers	ET + KT: ↓ VAS, WOMAC ↑ Serum COMP, plasma MMP-1 and MMP-3 ET: ↓ VAS, WOMA

							C ↑ Serum COMP, plasma MMP-1 and MMP-3
Gabrielli Vassão et al (2021) [50]	n = 42	Age 55 - 70 years Knee OA	Combined/multimodal	ESP: exercise protocol plus sham PBM irradiation EAP: exercise protocol plus active PBM Irradiation CG: no exercise	2 times weekly for 8 weeks	Pain Biomarkers	ESP: ↓ WOMAC, IL-1β, IL-10, IL-6, TNF-α ↑ CTX-II, IL-8 EAP: ↓ WOMAC, IL-1β, TNF-α ↑ CTX-II, IL-10, IL-6, IL-8 CG: ↓ WOMAC, CTX-II, IL-10, TNF-α ↑ IL-1β, IL-6, IL-8
Bandak et al (2021) [51]	n = 60	Age ≥ 40 years Knee OA	Combined/multimodal	ET = functional and individualized exercise therapy protocol CG = no exercise	3 times Weekly for 12 weeks	Pain Biomarkers	ET: ↑ KOOS ↓ IL-6, IL-10 CG: ↓ KOOS, IL-6, IL-10
Park et al (2021) [36]	n = 81	Age ≥ 60 years Knee OA Women	Resistance	ISOM = Isometric exercise protocol to 14-15 RPE ISOM + EMS = Isometric exercise protocol – 80% of 1MT - wearing a WB-EMS suit with electrical stimulation (85 Hz)	3 times Weekly for 8 weeks	Pain Functional assessment Biomarkers	ISOM: ↓ IL-6, TNF-α, CRP, RSTN ↑ KOOS, PT, PTBW ISOM + EMS: ↓ IL-6,

				CG = no exercise			TNF-α, CRP, RSTN ↑ KOOS, PT, PTBW CG: ↑ IL-6, TNF-α, CRP, RSTN ↓ PT, PTBW
Wang et al (2021) [37]	n = 143	Age over 60 years Knee OA	Combined Neuromuscular Resistance	CE = Quadriceps strengthening exercises protocol + Qigong BDJ = *Qigong:* Baduanjin qigong protocol QSE = Quadriceps strengthening exercises protocol	3 times weekly for 24 weeks	Pain	CE = ↓ WOMAC BDJ = ↓ WOMAC QSE = ↓ WOMAC
Rafiq et al (2021) [38]	n = 50	Age 45 – 60 years Knee OA	Resistance	IG= Strengthening exercise of the lower limb rehabilitation protocol CG = no exercise	3 times weekly for 4 weeks	Pain	RPG: ↓ WOMAC CG: ↓ WOMAC
Staushol m et al (2022) [47]	n = 50	Age ≥ 50 years Knee OA	Resistance	IG = Lower limb strength training + lower limb laser therapy at 45 joules per knee per session CG = Lower limb strength training + placebo lower limb laser therapy	3 times weekly for 8 weeks	Pain Functional assessment	IG: ↓ VAS, ↑ KOOS, 30s STS, knee AROM CG: ↓ VAS, ↑ KOOS, 30s STS, knee AROM
Zhang et al (2022) [48]	n = 50	Age 45-65 years Knee OA	Neuromuscular Stretching	IG: *Qigong:* YJJQE exercise protocol CG: *Stretching:* Stretching exercise protocol	2 times weekly for 12 weeks	Pain Functional assessment	YJJQE: ↓ WOMAC, VAS ↑ Berg balance Scale

							CE: ↓ WOMAC, VAS ↑ Berg balance Scale
Almeida et al (2022) [49]	n= 66	Age 50-80 years Knee OA	Resistance	G1 = multimodal training + hip abductor exercises G2 = multimodal training + hip adductor exercises	2 times weekly for 6 weeks	Pain Functional assessment	G1: ↓ pain NRS, TUG, ↑ KOOS, 30s STS G2: ↓ pain NRS, TUG, ↑ KOOS, 30s STS

Studies with PA protocol for chronic pain, functional assessments and biomarkers. Abbreviation: 1RM, one repetition maximum; 30" STS, 30 seconds sit to stand test; 6-MWT, 6-minute walking test; AROM, active range of movement; CG, control group; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; CTX-II, C-telopeptide of type II collagen; HADS, Hospital Anxiety and Depression scale; IG, intervention group; IL-, interleukins; KOOS, Knee Injury and Osteoarthritis Outcome Score; MMP-, matrix metalloproteinase; NRS, numeric rating scale; OA, osteoarthritis; PBM, photobiomodulation; PT, peak torque; PTBW, peak torque body weight; ROM, range of movement; RSTN, resistin; SF-12, Short-form survey 12; SPPB, short physical performance battery; sTNFR1-1, soluble tumor necrosis factor- α receptor-1; sTNFR-2, soluble tumor necrosis factor- α receptor-2; TNF- α, tumor necrosis factor-α; TST, time stands test; TUG, time up and go; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ↑, increase; ↓, decrease.

2.3.3 Risk of bias within studies and methodological quality

As above, studies with a high risk of bias in the third and fourth domains were not considered high risk overall. On the other hand, a high risk of bias in the domains 'incomplete outcome data' and 'selective reporting' resulted in an overall high risk. Nevertheless, after a critical review of each included study, it was concluded that all included studies could be considered to be of methodological and scientific quality (Fig. 2).

2.3.4 Variables

In the next paragraphs will be reported the outcomes analysed with their specifics assessments and the types of training proposed (Table 2).

Table 2. Summary of the studies reporting the effect of different type of exercise on the assessments related to pain, functional parameters and inflammatory biomarkers included in the review.

OUTCOMES	ASSESSMENT	TRAINING TYPE

PAIN	Western Ontario and McMaster Universities Osteoarthritis Index - WOMAC (n = 15); Visual Analogue Scale - VAS (n = 7); Numeric Rating Scale - NRS (n = 3); Knee Osteoarthritis Outcome Scale - KOOS (n = 6)	Neuromuscular [41] [42] [45] [46] [37] [48]
		Resistance [52] [41] [53] [54] [34] [44] [36] [37] [38] [47] [49]
		Aerobic [41]
		Combined [40] [42] [39] [43] [45] [46] [35] [50] [51] [37]
FUNCTIONAL ASSESSMENTS	6MWT (n= 4); TUG (n= 6); Stair climb (n= 3); 30" STS (n= 5); ROM (n= 2); Berg Balance scale (n= 2); Isokinetic strength (n= 1); Isometric strength (n= 1); Single leg stance (n= 1); Step (n= 2); 4 square step (n= 1); Knee flexion/extension strength (n= 1); Active knee flex/extension (n= 1); 1 RM (n= 2); TST (n= 1); Dynamic balance (n= 1); 10m walk (n= 1); Leg extension power (n= 1); 40 m walk (n= 1); PT and PTBW (n= 1); SPPB (n=1)	Neuromuscular [41] [42] [45] [46] [48]
		Resistance [52] [41] [53] [54] [34] [44] [36] [47] [49]
		Aerobic [41]
		Combined [40] [42] [43] [45] [46]
INFLAMMATORY BIOMARKERS	sTNFR1 and sTNFR2 (n= 1); serum CRP (n= 2); IL-6 (n= 4); IL-1 β (n= 1); IL-10 (n= 2); IL-8 (n= 1); TNF-α (n = 3); serum COMP (n= 2); CTX-II (n= 2); plasma MMP-1 and MMP-3 (n= 1); RSTN (n= 1)	Neuromuscular n.a.
		Resistance [52] [41] [54] [36]
		Aerobic [41]
		Combined [46] [35] [50] [51]

Abbreviation: OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; 6-MWT, 6-minute walking test; sTNFR1-1, soluble tumor necrosis factor- α receptor-1; sTNFR-2, soluble tumor necrosis factor-α receptor-2; NRS, numeric rating scale; TUG, time up and go; VAS, visual analog scale; 30" STS, 30 seconds sit to

stand test; CRP, C-reactive protein; IL-, interleukins; TNF- α, tumor necrosis factor-α; ROM, range of movement; AROM, active range of movement; COMP, cartilage oligomeric matrix protein; CTX-II, C-telopeptide of type II collagen; 1RM, one repetition maximum; TST, time stands test; HADS, Hospital Anxiety and Depression scale; SF-12, Short-form survey 12; SPPB, short physical performance battery; KOOS, Knee Injury and Osteoarthritis Outcome Score; MMP-, matrix metalloproteinase; PBM, photobiomodulation; PT, peak torque; PTBW, peak torque body weight; RSTN, resistin.

Pain

Pain was measured with one or more of the following instruments: Western Ontario and McMaster Universities Osteoarthritis Index - WOMAC (n = 15), Visual Analogue Scale - VAS (n = 7), Numeric Rating Scale - NRS (n = 2), Knee Osteoarthritis Outcome Scale - KOOS (n = 5).

Functional Assessment

The functional abilities were assessed through one or more of the following test: 6 Minutes Walking (6MWT) (n= 4), Time Up and Go (TUG) (n= 5), Stair climb (n= 3), 30" Sit to Stand (STS) (n= 4), Range of Motion (ROM) (n= 2), Berg Balance scale (n= 2), Isokinetic strength (n= 1), Isometric strength (n= 1), Single leg stance (n= 1), Step (n= 2), 4 square step (n= 1), Knee flexion/extension strength (n= 1), Active knee flex/extension (AROM) (n= 1), 1 Repetition maximum (RM) (n= 2), Time Stands (TST) (n= 1), Dynamic balance (n= 1), 10m walking (n= 1), Leg extension power (n= 1), 40 m walk (n= 1), peak torque (PT) and peak torque/body weight (PTBW) (n= 1), Short Physical Performance Battery (SPPB) (n=1).

Inflammatory Biomarkers

The studies identified in this review analysed one or more of the following biomarkers: TNF receptor 1 and 2 (sTNFR1;sTNFR2) (n= 1), serum C-reactive protein (CRP) (n= 2), IL-6 (n= 4), IL-1 β (n= 1), IL-10 (n= 2), IL-8 (n= 1), TNF-α (n = 3), serum cartilage oligomeric matrix protein (COMP) (n= 2), C-terminal cross-linked telopeptide of type II collagen (CTX-II) (n= 2), plasma matrix metalloproteinase 1 and 3 (MMP-1; MMP-3) (n= 1), resistin (RSTN) (n= 1).

2.3.5 Meta-analysis results on pain

A total of n=11 papers were included in the analysis (Fig. 1 and 3, table 3), using the individual interventions of each study as if they were separate studies, for a total of 22 studies.

The observed standardized mean differences ranged from -6.13 to -0.05, with most estimates being negative (100%). The estimated average standardized mean difference based on the random-effects model was -1.47 (95% CI: -2.09; -0.85). Therefore, the average outcome differed significantly from zero ($z = -4.64$, $p < 0.001$). According to the Q-test, the true outcomes appear to be heterogeneous ($Q(21) = 280.50$, $p < 0.001$, $tau^2 = 2.08$, $I^2 = 96\%$). In addition, since the I2 was too large (I2= 96%), it

was necessary to conduct a subgroup meta-analysis based on the type of training protocol proposed [55]

The overall ES, estimated through the Choen's d was -1,47 (95% CI: -2.09; -0,85; z = -4.63, p < 0.001). According to the Q-test, the amount of heterogeneity in the true outcomes was high (Q (21) = 280.497, p < 0.001, $tau^2 = 2.08$, $I^2 = 96\%$; H^2 24.71). A 95% prediction interval for the true outcomes is given by -4,542 to 1,602 (Fig. 3 and Table 3). Thus, the subgroup analysis generating the following values:

- Aerobic: ES -1,32 (95% CI: -2,14; -0,50) (z -4,638, p 0,002)
- Resistance: ES -1,45 (95% CI: -2,17; -0,72) (z -3,908, p <0,001)
- Neuromuscular: ES -2,26 (95% CI: -4,37; -0,14) (z -2,094, p =0,036)
- Combined: ES -0,85 (95% CI: -1,34; -0,35) (z -3,323, p <0,001)

Table 3. Subgroup meta-analysis results

Effect size estimates for individual studies									
	Study	Effect size	Errore std.	Z	Sig. (two tailed)	Confidence interval 95%		Weight	Weight (%)
						Lower	Upper		
NM	Bennell (2014) NM [41]	-0.65	0.22	-2.934	.003	-1.080	-0.22	0.469	5
	Cheung (2016) NM/Yoga [42]	-1.16	0.27	-4.307	<.001	-1.69	-0.63	0.464	5
	Lin (2020) NM/AVGs [45]	-0.05	0.22	-.205	.838	-0.48	0.39	0.469	5
	Wang (2021) NM [37]	-0.56	0.23	-2.472	.013	-1	-0.12	0.468	5
	Zhang et al (2022) NM [48]	-5.34	0.60	-8.836	<.001	-6.52	-4.15	0.408	4
	Zhang et al (2022) Stretch [48]	-6.13	0.68	-9.080	<.001	-7.45	-4.81	0.394	4
	General Neuromuscular	**-2.26**	0.08	-2.094	0.036	-4.37	-0.14		
RT	Bennell (2014) RT [41]	-0.77	0.21	-3.592	<.001	-1.19	-0.35	0.469	5
	Samut (2015) RT-Isok [53]	-1.51	0.41	-3.647	<.001	-2.32	-0.70	0.443	4
	Wang (2016) RT [54]	-2.89	0.29	-10.108	<.001	-3.45	-2.33	0.462	5
	Wang (2016) RT+WV [54]	-3.63	0.33	-11.038	<.001	-4.27	-2.98	0.456	5

	Branco Ferraz (2017) BF-RT [34]	-0.96	0.43	-2.171	.030	-1.78	-0.09	0.441	4
	Branco Ferraz (2017) HI-RT [34]	-0.97	0.47	-2.047	.041	-1.89	-0.04	0.433	4
	Branco Ferraz (2017) LI-RT [34]	-1.18	0.44	-2.661	.008	-2.04	-0.31	0.439	4
	Wang (2021) RT [37]	-0.56	0.22	-2.556	.011	-0.99	-0.13	0.469	5
	Rafiq (2021) RT [38]	-0.56	0.31	-1.780	.075	-1.18	0.06	0.458	5
	General Resistance	**-1.45**	0.37	-3.908	<.001	-2.17	-0.72		
AE	Samut (2015) AE [53]	-1.32	0.42	-3.169	.002	-2.14	-0.50	0.443	4
	General Aerobic	**-1.32**	0.42	-3.169	0.002	-2.14	-0.50		
COM	Cheung (2016) COMB [42]	-0.32	0.27	-1.198	.231	-0.85	0.20	0.464	5
	Zakir et al (2016) COMB [39]	-0.73	0.28	-2.651	.008	-1.28	-0.19	0.463	5
	Lin (2020) COMB [45]	-0.08	0.22	-.374	.708	-0.52	0.35	0.469	5
	Gabrielli Vassão (2021) COMB + PMB [50]	-1.49	0.44	-3.361	<.001	-2.36	-0.62	0.438	4
	Gabrielli Vassão (2021) COMB [50]	-1.28	0.43	-2.965	.003	-2.12	-0.43	0.441	4
	Wang (2021) COMB [37]	-1.45	0.24	-6.068	<.001	-1.92	-0.99	0.467	5
	General Combined	**-0.85**	0.25	-3.323	<.001	-1.34	-0.35		

Abbreviations: AE, aerobic; AVGs, active video games; BF, blood flow restriction; COMB, combined; HI, high intensity; LI, low intensity; NM, neuromuscular; RT, resistance; WV, whole body vibration.

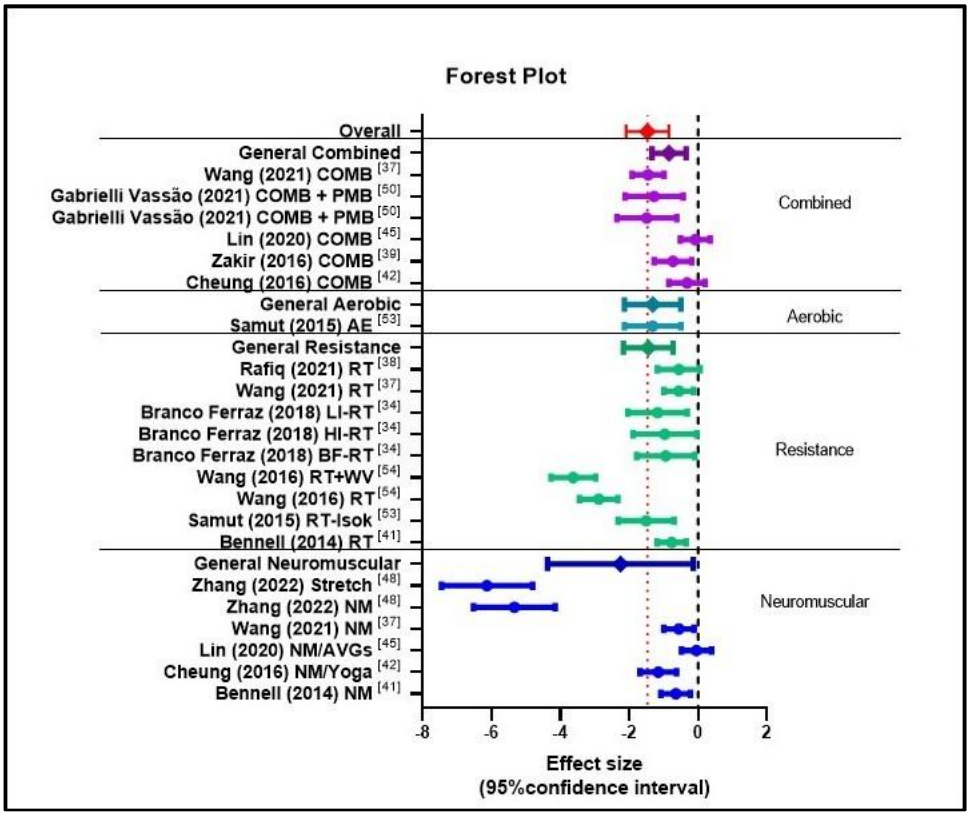

Fig. 3 Forest plot for meta-analysis conducted on pain.

2.4 Discussion

According to the last evidence PE is considered the most important non-pharmacological treatment of OA [15,17].

Pain, functional limitations, and inflammatory status, represents the three components of a vicious circle that characterized OA, and PE can act on all these elements [56]. Currently, it is clear that PE is able to reduce pain and activity limitations, and to improve participants' QoL in the short and long term [57]. Also, from an inflammatory point of view, adapted exercise can play an essential role in the prevention and treatment of OA by improving the inflammatory state [58].

Although exercise is now indicated in all guidelines on the treatment of OA, there is still no clear consensus on the administration of specific training protocols due to the difficulty of identifying which type of exercise intervention can generate the greatest benefits [59]. In fact, although some authors claim that new trials are not necessary to prove the effectiveness of exercise in OA [60,61], being able to find increasingly specific and effective protocols in the treatment and prevention of this condition, especially in different site from knee joint, remains a desirable goal in the field of adapted

PE. Therefore, a systematic review and meta-analysis of the literature from the last 14 years was conducted to investigate whether any new findings have emerged as to which type of exercise may generate a greater positive effect on pain perception, functional assessments, and inflammatory biomarkers in individuals with OA.

The meta-analysis was conducted on the pain outcome, creating subgroups by type of training. Although all interventions were able to reduce OA pain, neuromuscular training appeared to be more effective than the others. Indeed, although the major effect size was detected in the neuromuscular subgroup, the heterogeneity was too high, so it is not possible to reach conclusion about the effectiveness of this training type over the others. In addition, resistance training also seems to have a high effect on pain. However, differences in the parameters of protocol applied, such as intensity and frequency, and in the assessments used to evaluate the effects make difficult to compare interventions.

Moreover, for the analysis of the functional capacity and of the inflammatory biomarkers it was impossible to conduct a meta-analysis due to the heterogeneity of the test utilized. Thus, it was conducted a systematic review for both the outcome.

For functional capacity it was decided to divide the tests based on the general parameters: strength and power, functional abilities, and balance. Resistance, combined, and neuromuscular training all appear to improve strength. Specifically, these interventions demonstrated positive effects on isometric strength, knee flexion/extension strength, 1 RM, peak torque, and isokinetic strength. While resistance training is known for increasing strength, combined and neuromuscular training also appear to have beneficial effects.

For functional abilities, were included all those tests that give information on general fitness: aerobic capacity, mobility, coordination, flexibility, and walking speed. Also in this context, resistance, combined, neuromuscular, aerobic and dexterity training were able to improve general fitness and functional capacities of the participants enrolled.

Indeed, resistance training protocols seemed able to improve several different abilities evaluated through these tests: 6MWT, 30” STS, TST, Stair climb, 4 square step, knee AROM; similarly, combined training protocols were able to improve the TUG, 10 m and 40 m walking test, and Stair climb test; neuromuscular training protocols improved 4 square test, 40 m walking test, and Stair climb test; aerobic protocols improved 6MWT and 30” STS; and also active video games protocol was able to improve 40 m walking test and Stair climb test.

Effects on balance capacity were analysed after resistance training [41, 52] , neuromuscular training [41] and Qigong and stretching training [48], and combined training and active video game [45]. The study by Bennell et al 2014 [41] evidenced that the neuromuscular training group statistically improved the balance evaluated through the single leg stance, while the resistance training group showed a statistically significative decrease in the same parameter. However, except for the Bennell's study, all other studies showed an increase in balance capacity, either static or dynamic, after all protocols proposed.

Regarding the analysis of the inflammatory biomarkers that characterise OA, the framework is also difficult. Although the relationship between inflammation and OA was demonstrated, both for the pathogenesis of the disease and for the role it plays in pain symptoms, there is still no consensus on which inflammatory biomarkers may be the most effective in framing and monitoring the progress of the disease. Thus, the research area is still broad and wide-ranging. This is therefore also reflected in this review, in which studies that considered various inflammatory biomarkers related to OA were collected.

Unlike for pain and functional parameters, the variations of the inflammatory biomarkers were analysed only after resistance training [36, 49, 52, 53, 54], combined training [50, 51] and aerobic [53]. All studies on resistance training protocols showed a decrease of sTNFR2, CRP, TNF- α, serum COMP, CTX-II and RSTN, but contrasting results emerged on sTNFR1 and IL-6. Indeed, in the study of Simao et al 2012 [52], the authors analysed a resistance training protocol with and without a vibratory platform. This study showed an increase of the sTNFR1 only in the group without vibratory platform, but it's important to point out that the values at baseline in the group with vibratory platform were higher. In the resistance training protocols analysis, were found different results in the IL-6 trend after an isokinetic protocol [53] and an isometric protocol [36]. In the study of Samut et al 2015[53], higher levels of IL-6 were recorded after isokinetic training, while in the study of Park et al 2021[36] isometric training was able to reduce the levels of IL-6. These mixed results are difficult to compare, because, although the type of exercise is the same (resistance training), different training methods may inevitably lead to different results (isokinetic vs isometric). On the other hand, considering combined training, only IL-10 showed a statistically significative difference after the protocol, and most importantly due not to the type of intervention but to the addition of photobiomodulation [50]. Indeed, for the other biomarkers analysed, the trend is the same with a reduction of IL-1β, IL-6, and TNF- α, and an increase of CTX-II and IL-8 after training. Lastly, in this review, only one study analysed the effect of aerobic training on inflammatory biomarkers [53], showing a decrease of CRP, IL-6, and TNF- α. Thus, it confirms that physical exercise is an important modulator of inflammatory biomarkers in people with OA, although it has yet to be investigated in many aspects.

Lastly, what emerges from this review, is that neuromuscular training protocol seems to be the most effective in reducing pain, although resistance and combined training also show promising positive results; for the functional abilities and the inflammatory biomarkers all types of exercise were able to generate positive results, but there is a need to expand the research, both in terms of quantity and quality. Unfortunately, due to the small number of studies and the difference in the assessments used, it is still difficult to clearly evidence which type of intervention is the most effective to reduce pain and improve QoL in persons with OA. Furthermore, it is important to consider that some intervention types are less analysed than others, such as neuromuscular/sensorimotor training for inflammatory biomarkers, which seems promising due to its ability to reduce pain. In addition, people with chronic disease are more inclined to have a sedentary lifestyle, and therefore starting from low levels of physical activity allows positive results on pain and functional parameters with almost all training protocols, making it more difficult to determine which one may be the most effective [62]. This is also explained by the fact that pain and physical function at baseline moderate the effect of exercise on pain and physical function [63].

If we compare the results of this systematic review and meta-analysis with similar studies conducted previously, we can conclude that these results confirm the effectiveness of exercise in reducing OA-related symptoms [29]. At the same time, however, unlike the study by Juhl et al 2014 [30], these results emphasise the importance of neuromuscular training as the first type of training that people with OA should undergo. Furthermore, different from previous studies, this study also attempted to investigate the inflammatory aspect of exercise, and what emerges is the need to expand studies that also investigate the biomolecular response in exercise-related OA.

2.5 Conclusions

In addition to what has been noted by previous reviews, this manuscript highlights the key role of neuromuscular training, especially in knee osteoarthritis, although resistance training emerges as the most frequently studied intervention on pain. Most of the studies analysed are conducted on sedentary people, and this may mislead the results somewhat, as it is known that any type of physical activity induces benefits in the sedentary population. However, it seems that to have a real impact on pain in OA persons, neuromuscular and resistance components should be conducted consistently no less than twice a week, for at least 12 weeks, and using perceived pain as a parameter to modulate the workload. On the other hand, no clear results were found about the role of exercise in biomarker modulation related to pian, so further studies are needed in order to understand this relation especially in knee OA, which seems the most studied so far.

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CHAPTER 3

Second study

"Sensorimotor training in Osteoarthritis: effects of 24-weeks GYROKINESIS method® and Pilates on balance control, functional abilities and pain"

Accepted for publication in: Sports

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Abbreviations:

η^2p partial eta square

AP antero-posterior

BPI brief pain inventory

CI confidence interval

ES effect size

GK Gyrokinesis method

ICC Intraclass Correlation Coefficient

KOA knee ostearthritis

MF mean frequency

ML medio-lateral

MV mean velocity

OA osteoarthritis

PL Pilates

QoL quality of life

RMS root mean square

ROM Range of Motion

SF-36 36-item short form survey

TSK Tampa scale of kinesiophobia

TUG Time Up and Go

3.1 Introduction

Osteoarthritis (OA) is a degenerative joint disorder that affects ~8% of the global population [1] and the 15th leading cause of years lived with disabilities worldwide[2] [3]. Over the past 30 years, the number of OA diagnoses have increased by ~132% [4], with the knee joint being particularly susceptible [1] [5]. The pathophysiology of OA is characterised by the degradation of joint structures caused by a combination of mechanical stress and inflammation [2]. This can lead to symptoms including pain, stiffness, and swelling [6][7]. Collectively, these symptoms limit function and

mobility, disrupt daily activities, and negatively impact personal, social, and psychological well-being [7].

Individuals with knee OA often exhibit impaired balance control, characterised by increased postural sway, along with quadriceps weakness and reduced proprioception compared to age- and sex-matched controls [8]. These deficits are particularly evident in those experiencing higher levels of pain, who tend to show greater functional limitations and postural instability than asymptomatic individuals [9]. While pain and muscle strength are believed to influence balance control, further interventional research is needed to clarify these underlying mechanisms. Accordingly, promoting regular physical activity is likely crucial for improving clinical outcomes and mitigating fall risk in this population.

Pain is often identified as the most debilitating symptom of OA, triggering a negative cycle of muscle disuse, joint stiffness and reduced range of motion, which together further compromise balance and increase the risk of falls [10]. Exercise has emerged as a first-line, low-risk, and cost-effective strategy for reducing pain and improving physical function, balance and overall quality of life in individuals with OA [11] [12][13]. Both aerobic and strength exercises have been demonstrated to be effective in the management of OA symptoms [14]. However, a recent systematic review and meta-analysis suggests that neuromuscular or sensorimotor training, may be particularly effective in managing pain and improving physical function in individuals with OA[15][16]. Among these, Pilates (PL) is a widely practiced training approach that focuses on joint stability, posture, balance, and controlled movement [17]. Indeed, evidence suggests that as little as 8 weeks of Pilates training can significantly reduce pain and improve physical function and balance in patients with OA [17] [18].

Another emerging sensorimotor approach is the Gyrokinesis method (GY), which incorporates three-dimensional and spiral movements that integrate elements of yoga, dance and tai chi [19]. Similar to PL, GY also targets joint mobility, spinal articulation, postural control, and functional movement patterns and therefore has the potential to offer similar benefits to individuals with musculoskeletal disorders. Although research into Gyrokinesis is still in its early stages, preliminary studies have reported improvements in gait parameters (e.g., step length, stride length, gait speed) and lumbar stability after 4–8 weeks of training in individuals with low back pain [20][21]. Therefore, the primary aim of this exploratory study was to investigate the effect of a 24 weeks Gyrokinesis and Pilates intervention on balance control, functional parameters, pain, and kinesiophobia in individuals with knee OA. Additionally, we aimed to compare the outcomes between these two sensorimotor training modalities to evaluate their relative efficacy in alleviating OA-related symptoms.

3.2 Methods

3.2.1 Ethical approval

The study was approved by the ethical committee of the Lazio 1- San Camillo Hospital, Rome, Italy (Prot n 330/CE LAZIO 1 of 12th April 2023). All experimental procedures conformed to the Declaration of Helsinki, with the exception of prior registration in a public database [22]. All participants provided written informed consent before enrolment in the study.

3.2.2 Participants

Twenty female participants with knee osteoarthritis (KOA) were enrolled and completed the study (age: 60±7 years; weight: 68±10 kg; height: 165±6 cm; body mass index: 25±3 kg/m^2). Participants were aged between 45-70 years and took part in less than 50 minutes of moderate intensity exercise per week. All participants were diagnosed with grade 2 or 3 OA according to the Kellgren/Lawrence classification [23] and reported a Brief Pain Inventory (BPI) [24] score greater than 1.5. Exclusion criteria included other forms of arthritis, comorbidities, recent knee arthroplasty, and injuries. Participants on painkillers or anti-inflammatory drugs were required to maintain a consistent dosage throughout the study.

3.2.3 Experimental design

Participants were allocated non-randomly (based on geographical location) to either 24 weeks of GK (n=12) or Pilates (n=8). Over the 24 weeks, participants attended supervised sessions twice weekly (48 total sessions), in small groups (4-5 participants) at either 1-2pm or 4-5pm. Outcome measures were assessed before and after the intervention, with all assessments conducted between 8:00-10:00 to control for circadian rhythm effects on outcome measures.

3.2.4 Intervention characteristics

Gyrokinesis method training

Sessions were conducted by a licensed Level 1 trainer certified by the Gyrokinesis International Headquarters and followed the core principles of the method: synchronizing with corresponding breathing patterns, stabilization through opposition, joint space creation, scooping, and pelvis narrowing with lumbar spine decompression [20]. Training began with foot self-massage and progressed to isometric/dynamic lower limb exercises. Multidirectional spinal movements (arches, curls, spirals, circles) and abdominal engagement exercises ("seed centre connection") were included.

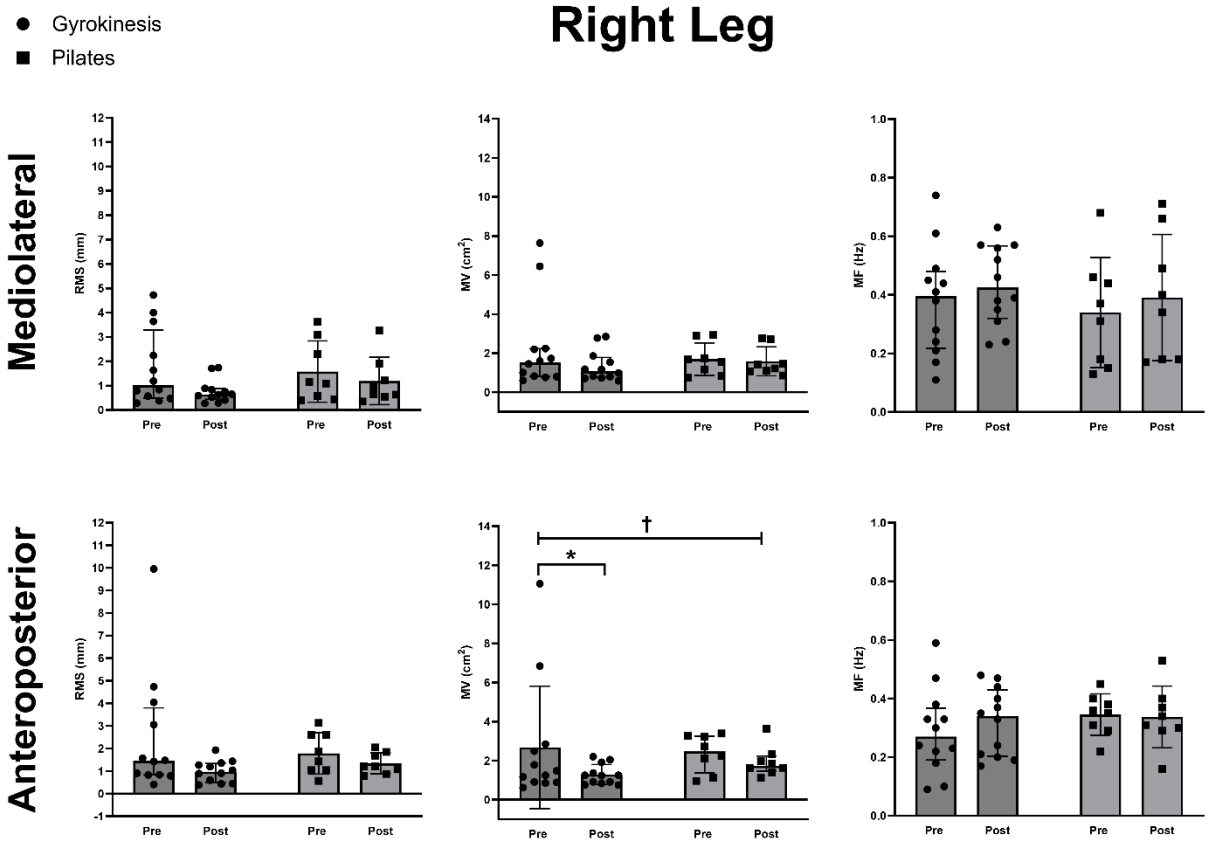
Sessions concluded with balance and proprioceptive tasks. Exercises were repeated 8–16 times and performed on a stool or mat (see Table 1 for full sequence).

Pilates training

Conducted by a certified Pilates instructor, sessions involved mat-based exercises in supine and standing positions. The program adhered to six core principles: concentration, centering, control, breathing, flow, and precision [25]. Training included breathing drills, core engagement, spinal mobility, standing balance work, and final flexibility-focused stretches. Unlike Gyrokinesis, Pilates exercises were segmented into discrete sets (8–16 repetitions) (see Table 1 for full sequence).

Table 1. List of exercises completed in each individual session for the Gyrokinesis group and Pilates group.

Pilates Mat	Gyrokinesis method
1. Warm-up	1. Arch & Curl series
2. Single leg stretch	2. Spiraling Twists
3. Double leg stretch	3. Sideways Arches
4. Criss-cross	4. Circles/Massaging the Organs
5. Single straight leg	5. Wave Series
6. Roll up	6. Leg/Hip Series
7. Rolling	7. Standing Series
8. Side kick: front/back	8. Cat Back Series
9. Side kick: small circles	9. Curl Back Series
10. Spine twist	10. Alternating Leg Series
11. Rowing 3	11. Scooping Wave Series
12. Rowing 4	12. Pulsation Series
13. Pull straps 1	13. Hip-Knee Mobilization Series
14. Pull straps 2	14. Arches/Back Strengthening
15. Swimming	15. Sphinx Series
16. Teaser 1	16. Abdominal Series
17. Leg pull back	17. Aerobic Class
18. Leg pull front	
19. Mermaid	
20. Rolling down	
21. Cool down	



3.2.5 Assessments

Postural sway

Postural sway was assessed using Microtech's Gyko[a] inertial sensor, positioned at the level of the fifth lumbar vertebra (L5) to the first sacral vertebra (S1). Participants performed a single-leg stance test on a firm surface, barefoot, with eyes open and arms by the sides. The test was performed on both the dominant and non-dominant leg, in a randomized order. Each trial lasted a maximum of 30 seconds. If participants lost balance, touched the ground with the non-stance foot, or used compensatory arm movements, the trial was terminated and the time to failure was recorded. Three trials were performed for each leg, and the best performance (i.e., longest stance time) was used for subsequent analysis.

Body sway parameters were extracted using the manufacturer's proprietary software and included root mean square (RMS), mean velocity (MV), and mean frequency (MF) in both anteroposterior and mediolateral directions. These metrics were chosen to capture distinct dimensions of postural control: RMS reflects sway amplitude/performance, MV quantifies sway speed, and MF estimates the frequency of postural adjustments. Although MV and MF both pertain to the temporal dynamics of sway, they provide complementary insights: MV reflects how rapidly the centre of mass shifts, while MF offers insight into the neuromuscular control strategies, particularly the rate of corrective adjustments. Despite some conceptual overlap, both parameters were retained due to their unique

contributions to understanding balance control in individuals with KOA. It is acknowledged that MV may be sensitive to test duration, as longer stance periods may lead to greater cumulative sway. Nonetheless, in populations with impaired balance, where sway tends to increase over time, MV may still capture meaningful differences in dynamic stability. In contrast, MF is considered less sensitive to test duration and more indicative of adaptive postural control mechanisms.

Functional measures

To assess physical function, flexibility, and range of motion, a battery of seven functional tests recommended by the Osteoarthritis Research Society International (OARSI) [26] was administered. Each test was performed three times, and the best attempt was recorded for analysis. Physical function was evaluated using four standardized tests: the Timed Up and Go (TUG), Stair Climb Test (10 steps), 30-Second Sit-to-Stand Test, and the 15-Second Step Test [27] [28]. Flexibility and range of motion were assessed using the Sit-and-Reach Test (targeting hamstrings and lower back), the Trunk Rotation Test (using the Gyko[a] sensor), and the Back Scratch Test, which evaluates scapulohumeral mobility [29] [30].

Perceptual measures (questionnaires)

The Italian version of BPI [24] was used to identify pain location, severity, and the extent to which pain interferes with daily activities, using a 0–10 Likert scale (0 = 'no pain' to 10 = 'the worst pain imaginable'). To assess kinesiophobia, the Italian version of the Tampa Scale for Kinesiophobia (TSK) was used [31]. This 13-item questionnaire evaluates ‘fear of movement’ based on activity avoidance and somatic focus. Quality of life was assessed using the SF-36 Health Survey, which measures self-reported health status across eight domains [32].

3.2.6 Statistical analysis

Data normality was assessed using the Shapiro-Wilk test. Parametric data were analysed using repeated measures two-way ANCOVA, with post intervention scores as the dependent variable, group as the fixed factor, and baseline values as covariates. The main effect of time was also examined and reported. For non-parametric data (BPI, TSK, SF-36, Stair Climb Test, Trunk Rotation Test, and all postural sway parameters except MF), Quade’s ANCOVA was applied: variables and covariates were ranked, residuals from linear regression were computed, and then analysed via one-way ANCOVA. Effect sizes were reported using partial eta squared (η^2p). Wilcoxon tests were used for within-group comparisons of non-parametric data. Parametric data were reported as means with 95% confidence

intervals, and non-parametric data as medians with interquartile ranges (Q1–Q3). Statistical significance was set at $P < 0.05$. Analyses were performed using SPSS[b] (v25.0, IBM Corp.) and GraphPad[c] Prism 10.

3.3 Results

3.3.1 Anthropometrics and characteristics

At baseline, there were no differences between groups in age (GK 58±7 years; PL 64±5 years; p=0.238), height (GK 166±6 cm; PL 164±7 cm; p=0.598), weight (GK 66±9 kg; PL 71±10 kg; p=0.248) and body mass index (GK 24±3 kg/m ^{2}; PL 26±3 kg/m ^{2}; p=0.062).

3.3.2 Postural sway

Right leg

Time of single leg stance

A difference between groups in the change over time was observed for the right single leg stance time (Quade's test: F(1,18)=5.50, p=0.031, η^2p=0.234) with a longer duration in the GK group. Within-group comparisons using Wilcoxon signed-rank tests showed no significant difference for both groups (GK: median 30 s, Q1-Q3=30–30, p=0.109, g=0.643; PL: median 30 s, Q1-Q3=22–30, p=0.273, g=-0.559).

Root mean square (RMS)

No differences between groups in change over time were apparent for ML (Quade's test: F(1,18)=1.61, p=0.221, η^2p=0.082) and AP (F(1,18)=1.99, p=0.175, η^2p=0.100) RMS.

Mean velocity (MV)

A difference between groups in the change over time was apparent for AP MV (Quade's test: F(1,18)=4.76, p=0.043, η^2p=0.209), whilst ML MV (Quade's test: F(1,18)=1.52, p=0.232, η^2p=0.078) showed no difference. Within-group analysis using Wilcoxon signed-rank tests revealed a reduction for the GK group for AP MV (median 1.24, Q1-Q3:0.87-1.64, p=0.028, g=-0.572), but not for the PL group (median 1.64, Q1-Q3:1.51-2.08, p=0.263, g=-0.440). Given the lack of significance for the ML direction, the within-group analysis was not conducted.

Mean frequency (MF)

No significant group × time interactions were found for MF in either ML ($F(1,18) = 0.17$, $p = 0.640$, $\eta^2p = 0.013$) or AP ($F(1,18) = 0.17$, $p = 0.730$, $\eta^2p = 0.007$) directions; post hoc tests were therefore not conducted.

The postural sway parameter graphs of the right leg are shown in Figure 1.

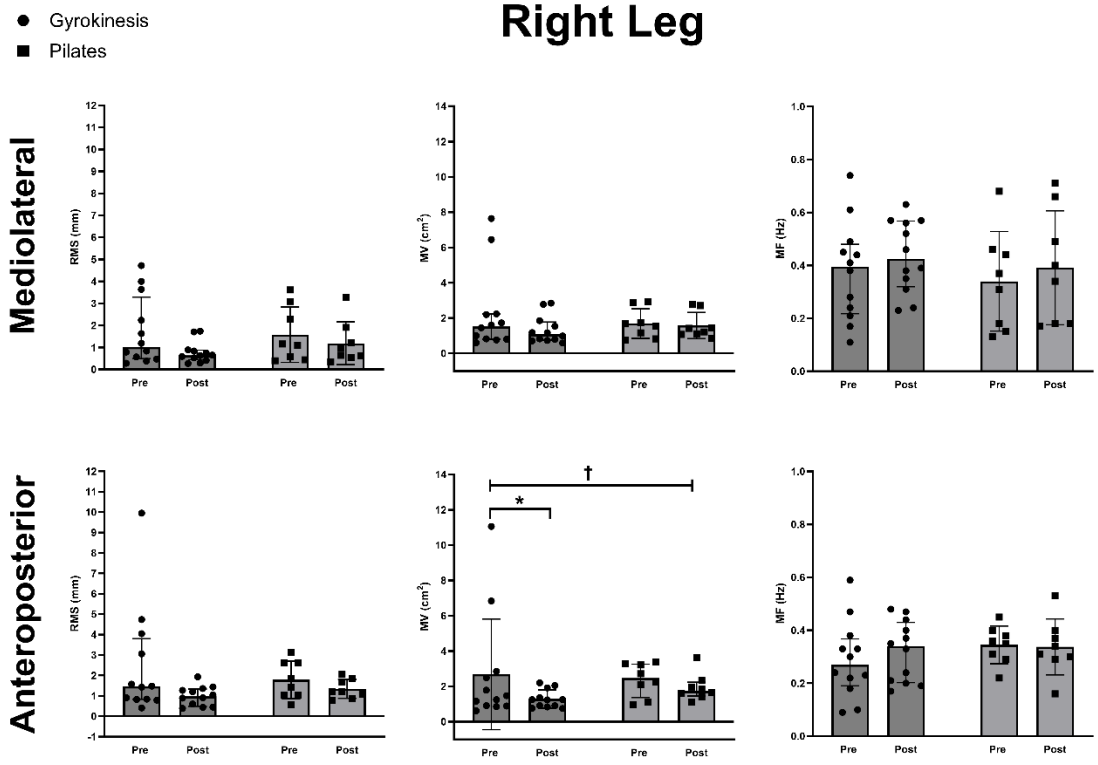


Fig. 1 *Right leg postural sway parameters, including mediolateral (a) root mean square (RMS) (b) mean velocity (MV) (c) mean frequency (MF) and anteroposterior (d) root mean square (RMS) (e) mean velocity (MV) (f) mean frequency (MF) for the Gyrokinesis group (n=12) and Pilates (n=8) groups before and after the 24-week intervention. Differences between groups in change over time are detonated as †=p<0.05 and within-group differences as *=p<0.05. Data are presented as median ± IQR.*

Left leg

Time of single leg stance

A difference between groups in the change over time was detected for the left single leg stance time (Quade's test: F(1,18)=11.93, p=0.003, η^2p=0.399) with a longer duration in the GK group. Within-group analysis using Wilcoxon signed-rank tests showed no difference for both groups (GK median 30 s, Q1-Q3=25-30, p=0.068, g=0.701; PL median 21 s, Q1-Q3=14-30, p=0.068, g=-0.439).

Root mean square (RMS)

There were no differences between groups in change over time for ML (Quade's test: F(1,18)=0.523, p=0.480, η^2p=0.030) and AP (Quade's test: F(1,18)=4.16, p=0.057, η^2p=0.197) RMS. Therefore, the post hoc analysis was not conducted.

Mean velocity (MV)

A difference between groups in change over time was found for both ML (Quade's test: F(1,18)=6.08, p=0.025, η^2p=0.263) and AP (F(1,18)=5.59, p=0.030, η^2p=0.348) MV. Within-group analysis using Wilcoxon signed-rank tests showed a reduction for the GK group in both ML (median 1.25, Q1-Q3:0.90 - 1.84, p=0.013, g=-0.700) and AP (median 1.24, Q1-Q3:0.96 - 1.62, p=0.008, g=-0.618) MV. No within-group differences were observed in the PL group for ML (median 1.83, Q1-Q3:1.14 - 3.12, p=0.249) and AP (median 2.55, Q1-Q3:1.29 - 3.91, p=0.128) MV.

Mean frequency (MF)

Mean frequency in AP and ML directions showed no time × group interactions (both P>0.05). Therefore, the post hoc analysis was not conducted.

The postural sway parameter graphs of the left leg are shown in Figure 2.

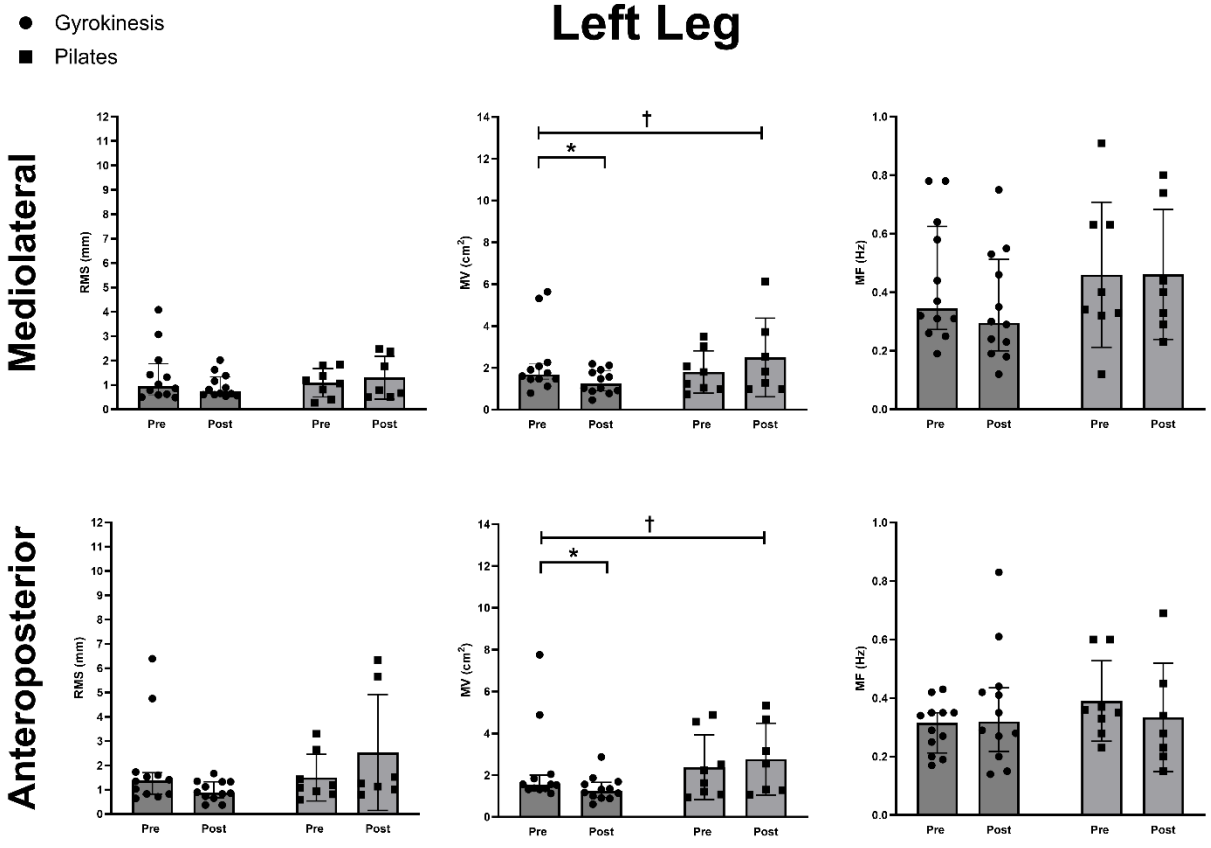


Fig. 2 *Left leg postural sway parameters, including mediolateral (a) root mean square (RMS) (b) mean velocity (MV) (c) mean frequency (MF) and anteroposterior (d) root mean square (RMS) (e) mean velocity (MV) (f) mean frequency (MF) for the Gyrokinesis group (n=12) and Pilates (n=8) groups before and after the 24-week intervention. Differences between groups in change over time are detonated as †=p<0.05 and within-group differences as *=p<0.05. Data are presented as median ± IQR.*

3.3.3 Physical function/Functional parameters

A significant group × time interaction was found for the 30-Second Sit-to-Stand test ($F(1,18)=35.152$, $p< 0.001$, $\eta^2p=0.674$). Post hoc analysis revealed a significant increase in the number of sit to stand repetitions in the GY group ($p<0.001$, $g=2.162$), but not the PL group ($p=0.879$). Similarly, a significant group × time interaction was observed for the TUG test ($F(1,18)=10.574$, $p=0.005$, $\eta^2p=0.383$), with a significant reduction in test execution time for the GY group ($p<0.001$, $g=-1.214$) and no significant change in the PL group ($p=0.426$). For the Step Test, a significant group × time interaction was observed for both the right and left leg (right: $F(1,18)=18.934$, $p<0.001$, $\eta^2p=0.527$; left: $F(1,18)=28.246$, $p<0.001$, $\eta^2p=0.674$). Post hoc comparisons indicated a significant increase in the number of steps in the GY group (both p's <0.001, right $g=1.794$), but not in the PL group (right: $p=0.742$; left: $p=0.976$). A difference between groups in the change over time was observed for the Stair Climb test (Quade's test: $F(1,18)=5.73$, $p=0.028$, $\eta^2p=0.241$). Follow-up within-group analyses using the Wilcoxon signed-rank test showed a significant reduction in test execution time in both groups (GY: $p=0.002$, $g=-1.527$; PL: $p=0.050$, $g=-0.811$). Main effects of time are reported in Table 2, but the focus remains on significant interactions and post hoc comparisons.

3.3.4 Range of motion and flexibility

A time × group interaction was observed for the scratch test on both sides (right: $F(1,18)=87.129$, $p<0.001$, $\eta^2p=0.837$; left: $F(1,18)=150.585$, $p<0.001$, $\eta^2p=0.899$). Post hoc analysis revealed a significant improvement in the shoulder range of motion on both sides for both groups (GY: right $p=0.038$, $g=-0.136$, left $p<0.001$, $g=-0.405$; PL: right and left $p<0.001$, right $g=-4.456$; left $d=-3.709$, $g=-3.507$). No significant interaction was observed for the Sit-and-Reach Test ($F(1,18) = 2.68$, $p = 0.120$, $\eta^2p = 0.136$), so no post hoc tests were conducted. There was no difference between groups in the change over time for the trunk rotation test on the right (Quade's test: $F(1,18)=3.58$, $p=0.075$, $\eta^2p=0.166$) or the left side (Quade's test: $F(1,18)=3.68$, $p=0.071$, $\eta^2p=0.170$). Therefore, no further within-group comparisons were performed. Main effects of time were also explored and are reported in Table 2.

Table 2. Before and after intervention assessments of physical function, range of motion and flexibility for the Gyrokinesis group (n=12) and Pilates (n=8) groups.

	Gyrokinesis (Mean, 95% CI; or Median, Q1-Q3)		Pilates (Mean, 95% CI; or Median, Q1-Q3)		Statistical significance and effects sizes			
Parameter	**Week 0**	**Week 24**	**Week 0**	**Week 24**	**Time x Group**	**η^2p (Time x Group)**	**Time**	**η^2p (Time)**
30" Sit to stand (rep)	13.83 (11.3 to 16.3)	24.33 (21.2 to 27.5)	11,29 (9,62 - 12,95)	11,71 (9,81 - 13,62)	**<0.001**	0.674	**0.008**	0.342
TUG (s)	5.8633 (5.3 to 6.4)	4.9 (4.5 to 5.3)	7,67 (6,52 - 8,83)	6,61 (5,89 - 7,33)	**0.005**	0.383	**0.001**	0.518
Step test right (rep)	14.08 (12.3 to 15.9)	18.9 (17.4 to 20.4)	9,29 (7,90 - 10,67)	11,14 (9,26 - 13,03)	**<0.001**	0.527	**<0.001**	0.528
Step test left (rep)	13.58 (11.9 to 15.3)	19.2 (17.9 to 20.6)	9,43 (7,84 - 11,02)	11,14 (9,11 - 13,17)	**<0.001**	0.674	**<0.001**	0.592
Stair Climb (s)	9 (8 - 9.9)	7.1 (6.2 - 7.6)	12.7 (11.5 - 12.9)	9.3 (8.8 - 9.7)	**0.028**	0.241	n/a	n/a
Scratch test right (cm)	23.750 (20.1 to 27.3)	23 (19.8 to 26.1)	30,00 (25,28 - 34,72)	11,79 (9,79 - 13,78)	**<0.001**	0.837	0.437	0.036
Scratch test left (cm)	28 (23.6 to 32.3)	25.5 (22.6 to 28.5)	33,43 (27,25 - 39,61)	14,21 (10,33 - 18,10)	**<0.001**	0.899	0.387	0.044
Sit and reach (cm)	2.2 (-3.8 to 8.2)	7.7 (3.0 to 12.3)	-2,00 (-9,18 - 5,18)	2,29 (-2,94 - 7,51)	0.120	0.136	**0.001**	0.512
Trunk rotation right (°)	37.5 (29.4 - 41.9)	50.7 (41.2 - 57.5)	37.9 (30.6 - 42.3)	40.1 (38.9 - 42.7)	0.075	0.166	n/a	n/a
Trunk rotation left (°)	31.4 (27.5 - 39.1)	49.7 (39.7 - 54.5)	36.3 (32.4 - 39.3)	42.7 (36.3 - 43.9)	0.071	0.170	n/a	n/a

3.3.5 Pain

A difference between groups in the change over time was observed in BPI scores, which indicated a significantly greater reduction in the GK group compared to the PL group (Quade's test: $F(1,18)=5.59$, $p=0.029$, $\eta^2p=0.237$). Indeed, within-group comparisons using Wilcoxon signed-rank tests showed a significant reduction in perceived pain in the GK group (median 0.45 a.u., Q1–Q3: 0.18–1.5 a.u., $p=0.002$, $g=-2.000$), but not in the PL group (median 3.6 a.u., Q1–Q3: 0.9–5.3 a.u., $p=0.327$) (Fig.3).

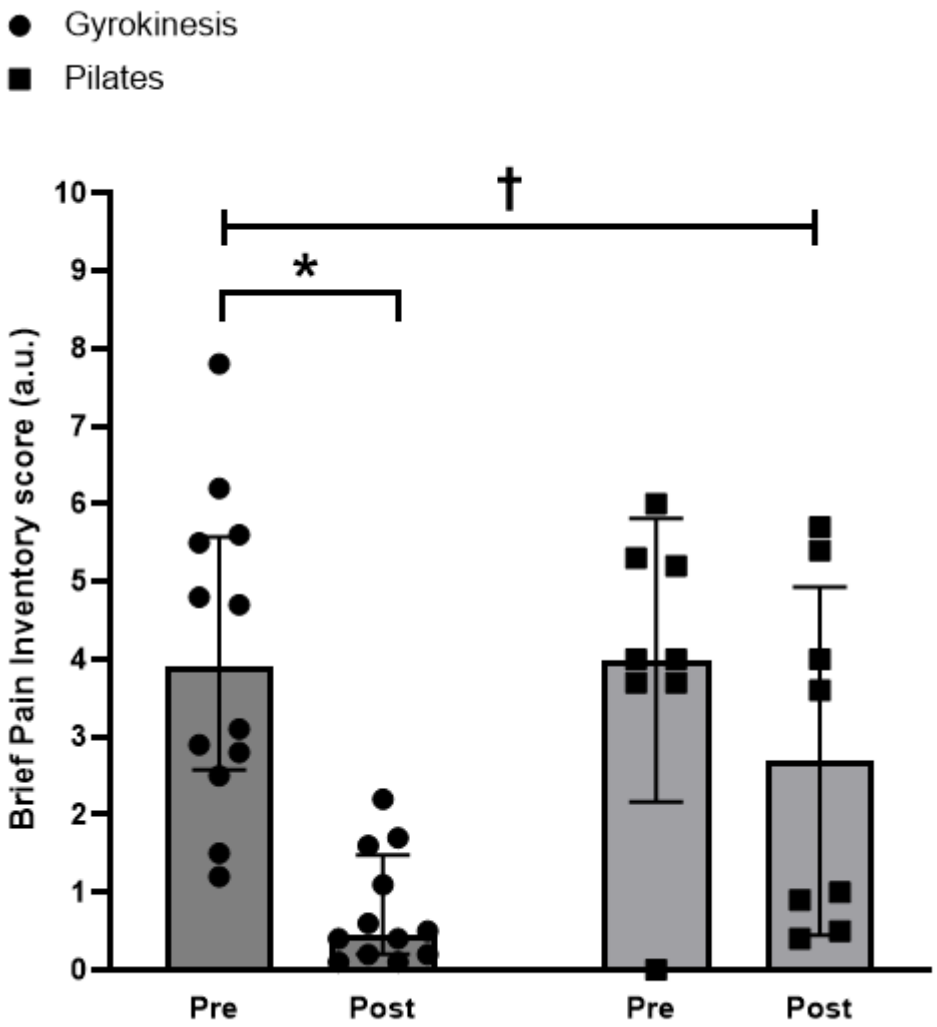


Fig.3 *Brief Pain Inventory score for the Gyrokinesis group (n=12) and Pilates (n=8) groups before and after the 24-week intervention. Differences between groups in change over time are detonated as (†=P<0.05) and within-group differences as (*=P<0.05). Data presented as median ± IQR.*

3.3.6 Kinesiophobia

No difference between groups in the change over time was observed for kinesiophobia scores (Quade's test: $F(1,18)=1.56$, $p=0.228$, $\eta^2p=0.080$). Therefore, no within group analysis was conducted.

3.3.7 Quality of Life

There were no differences between groups in the change over time for "Physical Health" (Quade's test: $F(1,18)=1.306$, $p=0.268$, $\eta^2p=0.68$) or "Mental Health" (Quade's test: $F(1,18)=3.780$, $p=0.068$, $\eta^2p=0.174$). Among the individual domains of the SF-36, only "Emotional well-being" showed a significant difference between groups (Quade's test: $F(1,18)=5.360$, $p=0.033$, $\eta^2p=0.229$), but within analysis showed no significant changes in both GK and PL groups ($p>0.05$).

3.3.8 Adherence

Adherence in the GK group was 89% and PL group 92%. Exercise sessions were missed due to lack of time, difficulty commuting, work responsibilities and family commitments. All participants enrolled in the study completed the 24-week intervention.

3.4 Discussion

To our knowledge, this is the first study to compare the effects of the Gyrokinesis method with standard sensorimotor care, represented here by Pilates, in women with KOA. Contrary to our hypothesis, participants in the GK group experienced significantly greater improvements in several clinical parameters. These included greater reductions in perceived pain, superior improvements in postural control, and enhanced outcomes in several functional performance tests.

The reduction in pain perception observed in both groups supports existing evidence that exercise is an effective non-pharmacological intervention for OA. However, only the GK group demonstrated a statistically and clinically significant decrease in pain (−81% vs −32%), exceeding established thresholds for a meaningful reduction in pain [33]. This greater analgesic effect may be attributable to the method's emphasis on three-dimensional, fluid movements, which may reduce joint compression and more effectively redistribute mechanical loads. In this regard, similar modalities, such as Tai Chi and yoga, have demonstrated postural realignment benefits [34], which help mitigate joint stress and decrease nociceptive input [35].

Notably, improvements in postural sway, particularly in single-leg stance time and sway velocity were observed only in the GK group. The concurrent reductions in pain and enhancements

in balance suggest that there could be a functional relationship between these two parameters. This hypothesis is supported by recent findings from Alshahrani and Reddy (2023) [36], who demonstrated that in individuals with bilateral KOA, quadriceps weakness is strongly associated with impaired postural stability, and that pain significantly mediates this relationship. Their study revealed that reduced quadriceps strength correlated negatively with postural sway variables ($r = -0.43$ to -0.51, $p < 0.001$), and that individuals with OA showed markedly greater sway and ellipse area compared to healthy controls. These findings highlight the complex interplay between muscular function, pain, and balance, reinforcing the idea that improvements in one domain, such as pain reduction, may facilitate compensatory gains in postural control.

Chronic joint pain in OA is known to disrupt proprioception, induce neuromuscular inhibition, and promote compensatory postural strategies, all of which contribute to increased postural instability [7][35]. In line with this notion, we observed reductions in anteroposterior and mediolateral sway velocities, which may indicate more efficient motor control strategies. It is also important to highlight that reductions in sway velocity occurred without changes in amplitude. These findings are suggestive of superior coordinated corrective actions and improved joint stability [37] [38], rather than an increased joint stiffness which can occur when OA becomes more debilitating

While static balance improvements are important, most falls occur during dynamic situations. Crucially, the step test showed improvements in both groups. These observations appear clinically relevant, as postural sway and dynamic balance measures are established predictors of fall risk [39][40], and individuals with OA are susceptible to falls. Thus, improvements in both static and dynamic balance may contribute to greater safety and functional independence in everyday activities.

Functionally, the GK group demonstrated superior improvements compared to the PL group in measures of strength, mobility and coordination (e.g., TUG, Stair Climb, Sit-to-Stand). While both interventions improved upper limb mobility, the GK group led to a wider range of benefits, broader functional gains. These outcomes may reflect the method's holistic movement approach, which engages the entire kinetic chain and integrates spinal mobility with extremity control. Future research should focus on characterizing the effects of the GK method from a biomechanical and physiological perspective, for example by examining force distribution, joint mechanical loading and postural alignment following this practice. Additionally, the greater pain reduction observed in the GK group may have increased movement confidence and effort, further supporting improved performance. However, no significant differences were observed in kinesiophobia. Nevertheless, it is plausible that a reduction in pain and improvements in motor control may improve kinesiophobia in other diseased populations or individuals with more severe OA than that used in the current study. In this regard, it is important to consider that we were likely not powered to detect changes in all of our outcome

measures and the small sample size may restrict the generalizability of our findings. Furthermore, while our sample focused exclusively on women, a population highly affected by OA, the efficacy of the GY method for males and different age groups in day to day life without supervision remains to be determined.

3.5 Conclusions

In conclusion, the Gyrokinesis method appears more effective than Pilates in improving pain perception, postural control, and physical function in women with KOA. The observed improvements in pain perception and balance suggests that the Gyrokinesis method may not only alleviate OA symptoms but also to enhance functional stability and reduce fall risk. These findings support the inclusion of Gyrokinesis method in multimodal rehabilitation programs and highlights the need for further research to elucidate its biomechanical and neurophysiological mechanisms.

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Competing interests No conflict of interest

Manufacturers and Nondrug Products: [a] Gyko inertial sensor, Microgate S.r.l., Bolzano, Italy; [b] SPSS Statistics, version 25.0, IBM Corp., Armonk, NY, USA; [c] GraphPad Prism, version 10, GraphPad Software, San Diego, CA, USA

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CHAPTER 4

Exploratory study results

"Movement Quality Matters: Divergent Inflammatory and Antioxidant Responses to Two Sensorimotor Exercise Interventions in Osteoarthritis"

This chapter presents the results of an exploratory study
on the effects of sensorimotor training
on inflammatory biomarkers and oxidative stress parameters

Biomarkers Exploratory Results

The participants who took part in the aforementioned study also underwent blood sampling before and after the intervention to assess their inflammatory profile and oxidative stress, thereby laying the groundwork for further investigation into the relationship between blood biomarkers and pain. Of the 20 subjects previously recruited, it was possible to analyse blood samples from 9 subjects in the GK group and 8 subjects in the PL group.

4.1 Introduction

What has recently been shown to influence pain in OA is the chronic inflammation of the affected joints and the immunologic-inflammatory processes that play a decisive role in the pathogenesis of OA. Indeed, infiltration of macrophages and T lymphocytes occurs in the synovial membrane, and there are increases in the concentrations of proinflammatory cytokines and chemokines in the synovial fluid and blood. Joint degeneration also results from matrix metalloproteinases, which are induced by inflammatory mediators such as interleukins (e.g., IL-6, IL-1β, IL-8) and tumour necrosis factor (TNF-α). Thus, this inflammatory and immune framework affects the development of pain by acting on the nervous system. In fact, these inflammatory mediators increase peripheral sensitisation of free endings in the joint, increasing perceived pain[1]. Numerous studies are currently underway to identify these potential biomarkers, although an effective and widely accepted conclusion has not yet been reached. As shown in a recent study by Munjal et al. (2019)[2], biomarkers of OA can be present in urine, blood, and synovial fluid; each sampling medium has advantages and disadvantages in terms of analytical effectiveness, specificity, and cost.

Synovial fluid is the first fluid initially altered in the pathogenesis of OA, although it is more difficult to measure, unlike blood and urine, which are easily accessible and mediate many immune and immunological pathways. Numerous studies have identified synovial or blood IL-6, IL-8, IL-10, and TNF-α as reliable biomarkers in monitoring OA, which correlate with pain and loss of function [3]. Additionally, Castrogiovanni et al. (2019)[4], examined the role of moderate physical activity (PA) on these synovial fluid biomarker levels, including IL-1, in rats with OA. They demonstrated that moderate PA significantly reduced the expression of IL-4, IL-10, and lubricin in animals. Furthermore, in a study aimed at investigating the sensitivity and reactivity of pain in OA[5], levels of IL-6 and TNF-α were shown to be higher in patients with OA than in healthy subjects; importantly, the biomarkers appeared to be associated to the pain stimulus.

In recent years, increasing evidence has highlighted the pivotal role of oxidative stress in the pathophysiology of OA. Among the main intracellular antioxidant systems, glutathione plays a central role. It exists in two states: the reduced form (GSH) and the oxidised form (GSSG). The

total glutathione content (tGSH) corresponds to the sum of these two forms, while the GSH/GSSG ratio serves as a sensitive indicator of the cellular redox state[6]. Under physiological conditions, a high GSH/GSSG ratio reflects a predominantly reducing intracellular environment, characterised by a high availability of GSH capable of neutralising reactive oxygen species (ROS) and protecting cellular components from oxidative damage. Conversely, a decrease in this ratio indicates GSH oxidation, accumulation of ROS, and impairment of the antioxidant defence system.

Specifically, in the cartilage and synovial tissue of patients with OA, reduced levels of GSH and a decreased GSH/GSSG ratio are frequently observed, leading to the activation of catabolic pathways and the loss of tissue homeostasis[7][8].

Moreover, redox imbalance has direct repercussions on chondrocyte function. Excess ROS activate transcription factors such as NF-κB and MAPK, which induce the expression of matrix-degrading enzymes, including matrix metalloproteinases (MMPs) and aggrecans. In addition, oxidative stress promotes chondrocyte senescence, apoptosis, and ferroptosis, further compromising the regenerative capacity of the articular tissue[7].

This oxidative environment is closely linked to the activation of inflammatory pathways. The main pro-inflammatory cytokines involved in OA, particularly IL-1β and TNF-α, not only enhance ROS production but also reduce the activity of endogenous antioxidant systems, including glutathione. This creates a vicious cycle in which oxidative stress amplifies the inflammatory response by stimulating the release of additional cytokines such as IL-6 and IL-8, which in turn sustain cartilage degradation. In this context, the anti-inflammatory cytokine IL-10 attempts to counteract the process, yet its effects are often insufficient compared with the strong pro-inflammatory drive mediated by IL-1β and TNF-α[9].

Cellular damage is also reflected by the release of cytoplasmic enzymes into the synovial fluid. Among these, lactate dehydrogenase (LDH) is a well-established marker of cell necrosis or lysis; it is also commonly associated with intra-articular tissue damage and inflammation, however, LDH is not specific to OA compared with other joint disorders. Creatine kinase (CK), on the other hand, is traditionally linked to muscle injury, but in some rheumatic conditions its levels may also vary, ranging from marked elevations in inflammatory myopathies to mild, exercise-related increases in degenerative joint diseases; however, its role as a direct marker in OA remains less well defined than that of LDH [10][11].

Overall, OA can be regarded as a condition in which oxidative stress and inflammation are tightly interconnected: pro-inflammatory cytokines stimulate ROS production, which subsequently enhances the inflammatory response, promotes matrix degradation, and contributes to cellular damage, as reflected by the release of enzymes into the synovial environment. From this

perspective, the evaluation of the glutathione system together with enzymatic markers such as LDH and the cytokine profile may provide valuable insights into disease progression as well as potential therapeutic strategies [9]. Moreover, it is therefore clear that the strong biochemical and molecular changes that characterise OA make it increasingly necessary to define biomarkers that are effective in predicting, tracking, and monitoring this disease.

4.2 Methods

4.2.1 Ethical approval

The study was approved by the ethical committee of the Lazio 1- San Camillo Hospital, Rome, Italy (Prot n 330/CE LAZIO 1 of 12th April 2023). All experimental procedures conformed to the Declaration of Helsinki, with the exception of prior registration in a public database. All participants provided written informed consent before enrolment in the study.

4.2.2 Participants and experimental design

The participant characteristics, experimental design, and details of the two proposed interventions are reported in the previous chapter, in the *Materials and Methods* section of the study *"Sensorimotor Training in Osteoarthritis: Effects of 24-weeks GYROKINESIS Method® and Pilates on Balance Control, Functional Abilities and Pain."*

4.2.2 a Cytokine assay

Circulating IL-1β and TNF-α levels were measured using a magnetic bead-based multiplex assay (Bio-Plex Pro™ Human Cytokine, Chemokine assay, Bio-Rad Laboratories, Inc.) according to the manufacturer's protocol. A broad sensitivity range of standards (between 1.95 and 10,000 pg/ml; Bio-Rad Laboratories, Inc.) was used to quantify cytokine concentrations to ensure high assay sensitivity. Data acquisition was performed by Bio-Plex 200 System™ (Bio-Rad Laboratories, Inc.). Data analysis was performed by Bio-Plex Manager™ 6.0 software (Bio-Rad Laboratories, Inc.). Serum samples were run in triplicate.

4.2.2 b Creatine kinase and lactate dehydrogenase activity

Plasma creatine kinase (CK) activity was determined spectrophotometrically, according to manufactory recommendations, by a manual procedure using a commercial test kit (Greiner Diagnostic GmbH, Bahlingen-Gremany). Briefly, 50 microlitres of plasma were incubated in

Hexokinase-Glucose 6 Phosphate-G6P Dehydrogenase buffer for 3 minutes, NADPH production was subsequently followed at 340 nm for a further 3 minutes.

Plasma lactate dehydrogenase (LDH) activity was determined spectrophotometrically by quantifying the reduction of NAD+ (measured at 340 nm) at 30°C in an assay mixture containing 0.2 M Tris-HCl (pH 7.6), 7 mM oxidised NAD+, and 55 mM lactate with a 20 microlitres sample.

Millimolar extinction coefficient E340 = 6.22. One unit of enzymatic activity was defined as the amount of enzyme that forms 1 micromol of product per minute.

4.2.2 c Glutathione homeostasis

Blood reduced (GSH) and oxidised (GSSG) glutathione content was quantified by a 5,5′-Dithiobis(2-nitrobenzoic acid)-glutathione reductase recycling assay. Briefly, 100 microlitres of blood were deproteinized with 5% 5-sulfosalicylic acid, centrifuged, and the deproteinised supernatant solution obtained was collected and utilised for the assay. Oxidised glutathione (GSSG) was measured in samples where reduced GSH was masked by pretreatment with 2-vinylpyridine (2%). Ten microlitres of the sample were added to the reaction buffer (700 microlitres nicotinamide adenine dinucleotide phosphate (NADPH) (0.3 mM), 100 microlitres DTNB (6 mM), and 190 microlitres H2O). The reaction was started by adding 2.66 U/mL glutathione reductase and followed at 412 nm by the TNB stoichiometric formation. Samples of delta optical density (deltaOD)/min412 were compared to glutathione standards.

4.2.3 Statistical analysis

Statistical analyses were performed using non-parametric tests due to the small sample size and the non-normal distribution of the data.

Within-group differences between pre- and post-intervention measurements were assessed using the Wilcoxon signed-rank test. To evaluate between-group differences, change scores (Δ = post - pre) were calculated for each participant, and comparisons between groups were conducted using the Mann-Whitney U test for independent samples.

Statistical significance was set at $p < 0.05$. All analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA).

4.3 Results

4.3.1 Inflammatory markers - Interleukin 1 beta and tumour necrosis factor alpha

Figure 1 and Table 1 show the median ± IQR values of interleukin 1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) in the Gyrokinesis (GK, n = 9) and Pilates (PL, n = 8) groups before and after the 24-week intervention.

In the Gyrokinesis group, IL-1β levels significantly increased from 6.50 ± 1.00 to 9.00 ± 2.00 (p = 0.020), while TNF-α rose from 6.00 ± 0.50 to 7.00 ± 7.00 (p = 0.018). Similarly, in the Pilates group, both IL-1β and TNF-α concentrations showed significant increases after training, rising from 6.00 ± 0.50 to 11.50 ± 5.98 (p = 0.023) and from 6.00 ± 2.13 to 11.50 ± 5.25 (p = 0.039), respectively.

When considering the pre–post intervention changes (Δ) reported in Table 2, IL-1β showed a median increase of +1.0 in the Gyrokinesis group and +3.5 in the Pilates group, while TNF-α increased by +1.5 and +6.5, respectively. Although these differences between groups did not reach statistical significance (p = 0.063 for IL-1β and p = 0.107 for TNF-α), the magnitude of change was greater in the Pilates group, suggesting a more pronounced inflammatory response.

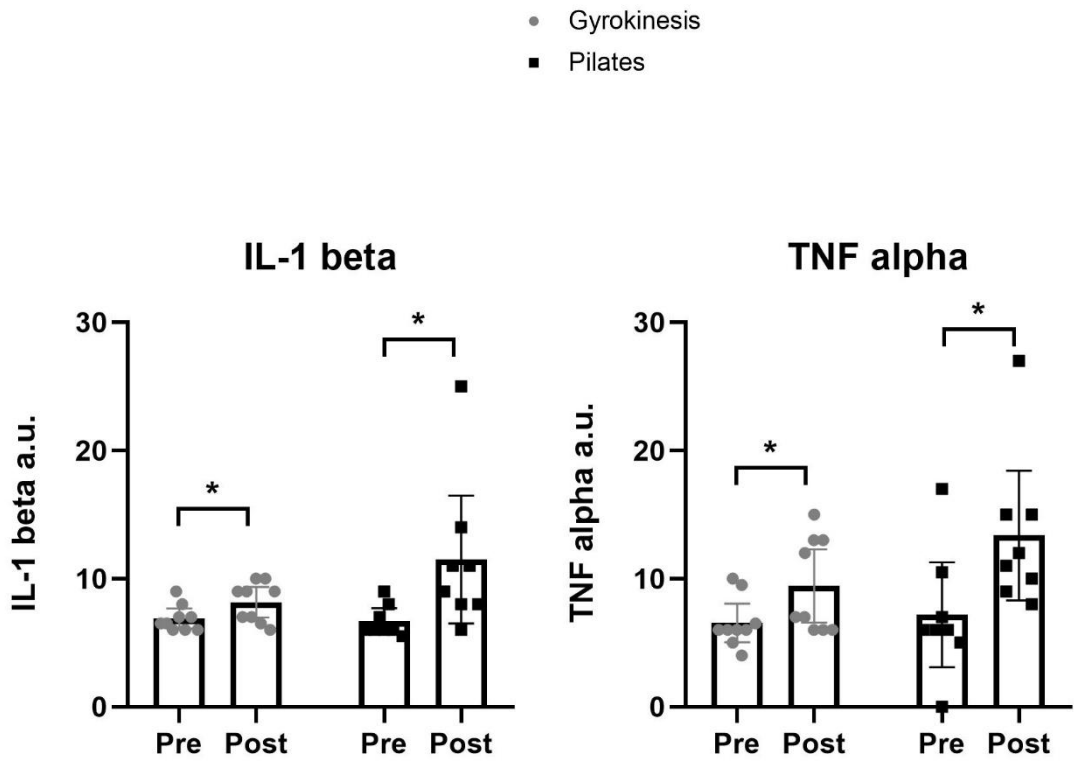

*Fig. 1 Interleukin 1 beta and tumour necrosis factor alpha levels for the Gyrokinesis (n=9) and Pilates (n=8) groups before and after the 24-week intervention. Differences between groups in change over time are detonated as †=p<0.05 and within-group differences as *=p<0.05. Data are presented as median ± IQR.*

	GK=9			***PL=8***		
	Pre	***Post***		***Pre***	***Post***	
	median ± IQR	***median ± IQR***	***p-value***	***median ± IQR***	***median ± IQR***	***p-value***
IL 1 beta	6.50 ± 1.00	9.00 ± 2.00	**0.020**	6.00 ± 0.5	11.50 ± 5.98	**0.023**
TNF alpha	6.00 ± 0.5	7.00 ± 7.00	**0.018**	6.00 ± 2.13	11.5 ± 5.25	**0.039**

Table 1 reports the median ± IQR values of inflammatory markers in the two groups (Gyrokinesis, GK, n = 9; Pilates, PL, n = 8) before and after 6 months of training.

	GK=9	***PL=8***	
	Δ median	***Δ median***	***p-value Δ***
IL 1 beta	+1.0	+3.5	0.063
TNF alpha	+1.5	+6.5	0.107

Table 2 presents the pre–post intervention changes (Δ) in inflammatory markers for the two groups (Gyrokinesis, GK, n = 9; Pilates, PL, n = 8), along with the corresponding p values.

4.3.2 Oxidative stress and cellular damage markers

Figure 2 and Table 3 summarize the changes in oxidative stress indicators and cell damage markers (tGSH, GSSG, GSH/GSSG, LDH, and CK) in both groups over the 24-week training period.

In the Gyrokinesis group, total glutathione (tGSH) levels increased significantly from 1513.61 ± 130.67 to 1693.28 ± 400.18 (p = 0.050), whereas in the Pilates group, a significant reduction was observed (from 1619.78 ± 330.76 to 1415.60 ± 245.00, p = 0.049). The change in tGSH (Δ) differed significantly between groups (+196 in Gyrokinesis vs. -179.67 in Pilates, p = 0.025), indicating an improvement in antioxidant capacity following Gyrokinesis training (Table 4).

No significant within-group changes were found for oxidized glutathione (GSSG) or the GSH/GSSG ratio, although the Gyrokinesis group showed a tendency toward improved redox balance (Δ GSH/GSSG = +4.59) compared with Pilates (Δ = -5.25, p = 0.123).

Markers of cell damage, lactate dehydrogenase (LDH) and creatine kinase (CK), did not show significant pre/post differences in either group. LDH tended to decrease slightly in the Gyrokinesis group (p = 0.051), whereas no meaningful changes were observed in the Pilates group.

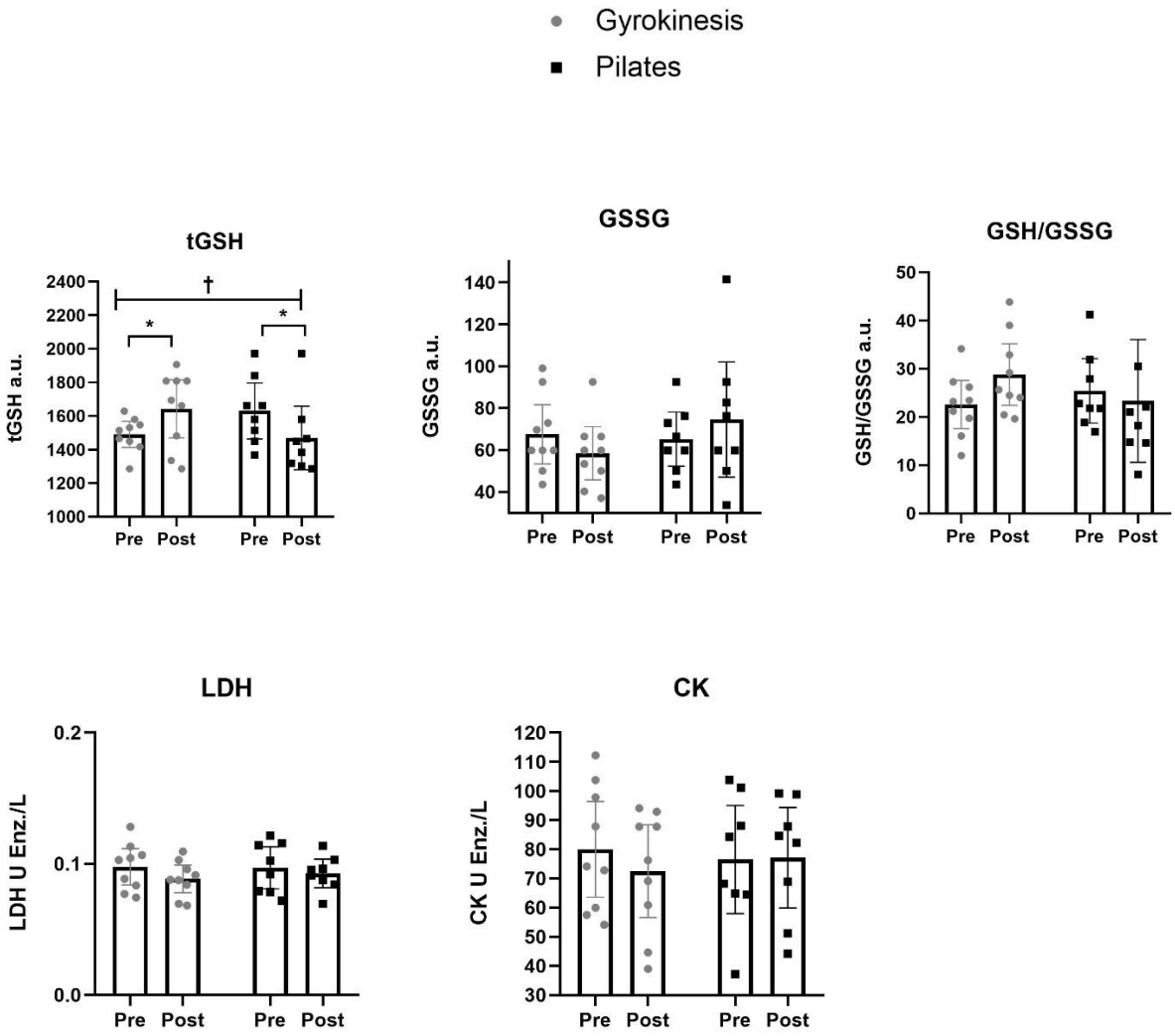

*Fig. 2 tGSH, GSSG and GSH/GSSG levels for the Gyrokinesis group (n=9) and Pilates (n=8) groups before and after the 24-week intervention. Differences between groups in change over time are detonated as †=p<0.05 and within-group differences as *=p<0.05. Data are presented as median ± IQR.*

	GK=9			***PL=8***		
	Pre	***Post***		***Pre***	***Post***	
	mediana ± IQR	***mediana ± IQR***	***p-value***	***mediana ± IQR***	***mediana ± IQR***	***p-value***

tGSH	1513.61 ± 130.67	1693.28 ± 400.18	**0.050**	1619.78 ± 330.76	1415.60 ± 245	**0.049**
GSSG	59.89 ± 27.76	59.89 ± 21.23	0.327	63.15 ± 22.86	68.05 ± 37.56	0.325
GSH/GSSG	23.18 ± 8.81	25.63 ± 13.71	0.110	22.29 ± 11.32	19.60 ± 13.74	0.327
LDH	0.10 ± 0.02	0.08 ± 0.02	0.051	0.09 ± 0.03	0.09 ± 0.01	0.674
CK	74.13 ± 42.11	76.25 ± 37.64	0.260	76.24 ± 33.28	83.44 ± 40.51	1.000

Table 3 reports the median ± IQR values of oxidative stress indicators and cell damage markers in the two groups (Gyrokinesis, GK, n = 9; Pilates, PL, n = 8) before and after 6 months of training.

	GK=9	***PL=8***	
	delta mediana	***delta mediana***	***p-value delta***
tGSH	+196	-179.67	**0.025**
GSSG	-11.43	+9.8	0.176
GSH/GSSG	+4.59	-5.25	0.123
LDH	-0.01	-0.0008	0.674
CK	-18.93	-9.13	0.484

Table 4 presents the pre–post intervention changes (Δ) in oxidative stress and cell damage markers for the two groups (Gyrokinesis, GK, n = 9; Pilates, PL, n = 8), along with the corresponding p values.

4.3.3 Exploratory correlations between pain and tGSH

In the Gyrokinesis (GK) group, a weak negative correlation was observed between changes in pain intensity and total glutathione (tGSH) levels (Figure 3, $y = -0.0026x - 2.2038$; $R^2 = 0.0709$). This trend suggests that greater increases in tGSH were associated with slightly larger reductions in perceived pain.

Conversely, in the Pilates (PL) group, the correlation between Δ pain and Δ tGSH was positive (Figure 4, $y = 0.0072x - 0.1415$; $R^2 = 0.3244$), indicating that participants with higher increases in tGSH tended to show smaller decreases or even slight increases in pain levels.

Although these relationships did not reach statistical significance, the opposite trends observed between the two exercise modalities may reflect distinct physiological adaptations. The negative association in the GK group could suggest a more effective antioxidant response, as increased tGSH, an important marker of redox balance, might contribute to reduced oxidative stress and consequently

to pain alleviation. In contrast, the positive trend in the PL group may indicate a different or delayed oxidative adaptation to the intervention.

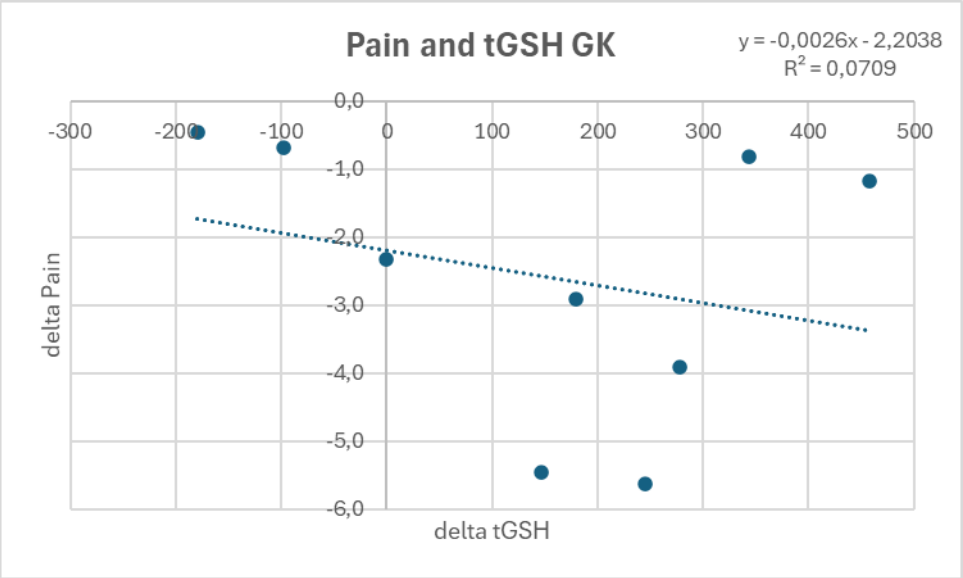

Figure 3. Scatter plot showing the relationship between changes in pain intensity (Δ pain) and total glutathione (Δ tGSH) levels in the GK group. A slight negative correlation was observed, as indicated by the regression line ($y = -0.0026x - 2.2038$; $R^2 = 0.0709$).

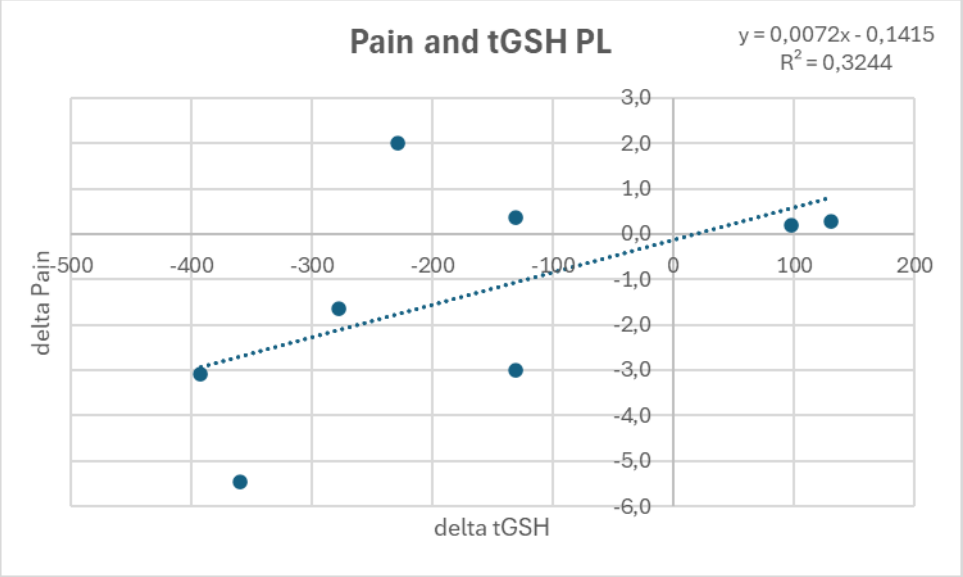

Figure 4. Scatter plot showing the relationship between changes in pain intensity (Δ pain) and total glutathione (Δ tGSH) levels in the PL group. A positive correlation was observed, as indicated by the regression line ($y = 0.0072x - 0.1415$; $R^2 = 0.3244$).

4.4 Discussion

The preliminary results of this study indicate significant differences between and within groups in the effects of two sensorimotor exercise interventions (Gyrokinesis and Pilates) on pain perception, functional parameters, serum levels of the pro-inflammatory cytokines IL-1β and TNF-α, and tGSH.

After 6 months of training, the Gyrokinesis group showed both clinically and statistically significant improvements in pain reduction and functional tests (30-second sit-to-stand, TUG, stair climb, ROM, and static and dynamic balance). The Pilates group did not reach statistical significance for the same parameters. Both groups exhibited an increase in serum IL-1β and TNF-α, which was more pronounced in the Pilates group. For oxidative stress parameters, tGSH increased in the GK group and decreased in the PL group, indicating better antioxidant protection in GK.

This pattern suggests that, although sensorimotor training may be associated with a measurable systemic inflammatory response, the quality of movement and specific characteristics of the exercise practice strongly influence both clinical and biological responses. Specifically, the Gyrokinesis method is characterised by dynamic, fluid, continuous, three-dimensional, and rhythmic movements integrated with conscious deep breathing. This practice may promote positive regulation of the autonomic nervous system, particularly by activating the parasympathetic (vagal) system involved in inflammation modulation[12]. Such vagal activation may help contain the production of IL-1β and TNF-α, two key pro-inflammatory cytokines involved in pain and OA progression. By contrast, Pilates, while still an effective and controlled form of exercise, relies more heavily on isometric contractions and core stabilisation, which may impose a more localised and potentially stressful mechanical load on already compromised joints.

The differing magnitude of the inflammatory response observed between the two groups suggests that increases in cytokine levels should not be interpreted univocally as signs of clinical deterioration. Instead, a moderate inflammatory response may reflect a physiological adaptation to exercise. The extent and clinical relevant of this increase depend on movement quality, autonomic modulation capacity, and the immune system’s sensitivity to physical activity.

Similarly, oxidative stress and cell damage markers show distinct patterns. In the GK group, a mild increase in tGSH and the GSH/GSSG ratio, with a stable or reduced GSSG, indicates an improved antioxidant defence. CK and LDH decreased slightly, consistent with the observed reduction in muscle and cytolytic damage. In the PL group, tGSH and the GSH/GSSG ratio decreased, while GSSG and CK increased, reflecting a worsened redox balance and greater muscle injury. These observations are consistent with the pathogenic role of ROS in OA described by Wojdasiewicz et al. (2014)[9] and the effects of NO-derived peroxynitrite on DNA and telomere erosion[13].

In line with these biochemical changes, the analysis of correlations between ΔtGSH and ΔPain revealed opposite patterns in the two groups. In the Gyrokinesis group, increases in tGSH were weakly but consistently associated with greater reductions in pain, supporting the protective role of glutathione against oxidative stress. In contrast, in the Pilates group, pain reduction was not directly associated with increases in tGSH, suggesting that this modality may not substantially influence redox balance. Instead, its analgesic effects may arise through alternative mechanisms, such as neuromuscular adaptations, improved biomechanics, or central modulation of pain perception. These divergent trends emphasize that the two exercise modalities may act through distinct biological pathways, with Gyrokinesis promoting a redox-related benefit and Pilates relying more on non-antioxidant mechanisms.

Overall, these findings support the hypothesis that sensorimotor exercise can modulate the inflammatory response and pain perception in individuals with OA and highlight how the qualitative characteristics of movement (e.g., Gyrokinesis) may offer a more favourable profile in terms of systemic adaptation, joint functionality, and containment of cytokine activation. These results encourage the integration of rhythmic, breath-based, and proprioceptive exercise modalities into OA management, moving beyond the purely quantitative prescription of physical activity.

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CHAPTER 5

Third study

“Feasibility and Preliminary Effects of a 12-Week Sensorimotor Training Program in Women with Fibromyalgia: A Proof-of-Concept Pilot Study”

In press:

Parisi A, Mauri C*, Del Mese C, Saliola M, Fiore D, Cerulli, Grazioli E

Feasibility and Preliminary Effects of a 12-Week Sensorimotor Training Program in Women with Fibromyalgia: A Proof-of-Concept Pilot Study.

In press on Medicina dello Sport 2025 ref. MSP012/25

5.1 Introduction

Fibromyalgia (FM), or fibromyalgia syndrome, is a relatively common condition, with an estimated prevalence of approximately 2% in the general population [1]. Despite its frequency, the clinical recognition of FM remains a considerable challenge for both patients and healthcare providers. The diagnostic process is often prolonged and complex; it may take over two years to establish a definitive diagnosis. This delay is associated with a high consumption of healthcare resources, even several years prior to diagnosis, compared to individuals without FM [2]. Although chronic pain is the hallmark symptom, it is not the only factor that impacts quality of life: fatigue, non-restorative sleep, mood disturbances, intestinal disorders and cognitive impairments are frequently reported and contribute to the heterogeneous and multifaceted nature of the condition [3].

Unlike nociceptive pain conditions such as osteoarthritis, the pain experienced in FM is primarily attributed to central sensitisation, a dysfunction in the way the central nervous system processes sensory information. Central sensitisation explains the discrepancy often observed between the severity of symptoms and the absence of detectable peripheral damage in FM, as well as the diffuse and persistent nature of the pain [4,5].

In 2016, the European League Against Rheumatism (EULAR) [6] updated its recommendations for the management of fibromyalgia (FM), emphasizing a personalized and multidisciplinary approach. These guidelines advocate for non-pharmacological strategies as first-line treatment, with patient education and physical exercise as key components. Among these, exercise is the only intervention strongly recommended, supported by robust evidence for its effectiveness in reducing pain and fatigue and improving sleep quality.

The guidelines also call for further research to compare different exercise modalities and assess the value of multimodal interventions. Numerous studies have confirmed the benefits of physical activity programs, particularly aerobic and resistance exercises, in improving pain, fatigue, sleep quality, and overall well-being in individuals with FM [7,8]. However, exercise modalities specifically targeting body awareness and motor control, such as neuromuscular or sensorimotor training, remain underexplored.

Emerging pilot studies suggest that sensorimotor interventions, which aim to enhance proprioception, balance, and neuromuscular control, may offer additional benefits by addressing altered sensorimotor integration often associated with central sensitization [9]. Despite these potential advantages, sensorimotor training is still rarely used in FM, especially regarding its impact on psychophysical aspects such as sleep quality, quality of life, and kinesiophobia.

In this context, it is worth noting that higher levels of physical activity are linked to improved quality of life in people with FM, partly due to reduced perceptions of fatigue [10]. Yet, many patients tend to reduce their daily activity levels or avoid exercise altogether, fearing symptom exacerbation [11]. This behavior, often driven by kinesiophobia, contributes to a pattern of predominantly light activity and prolonged sedentary behavior, leading to physical deconditioning [12].

These considerations highlight the need for tailored physical activity programs that account for the specific limitations and capabilities of people with FM. To this end, this pilot study investigates the feasibility and adherence to a 12-week sensorimotor training program in FM patients. In addition, the study explores its effects on pain, functional fitness, and related psychological outcomes. Findings may support the integration of sensorimotor training into clinical practice, offering a more holistic and cost-effective approach to FM management and informing future large-scale research.

5.2 Method

5.2.1 Ethical approval

All experimental methods conformed to the Declaration of Helsinki, with the exception of prior registration in a public database [13]. All participants provided written informed consent before enrolment on the study.

5.2.2 Participants

Five women with FM (age 56 ± 7.7 years; BMI 28.6 ± 8.3 kg/m²) were recruited. Inclusion criteria included age 40–65, clinical diagnosis of FM, chronic pain, and low physical activity levels (<150 min/week). Exclusion criteria included cardiovascular comorbidities or contraindications to exercise. Medication regimens were maintained throughout the study. Participant characteristics are shown in Table 1.

Table 1. Baseline characteristics. Abbreviations: SD, standard deviation; BMI, body mass index; BPI. Brief Pain Inventory questionnaire; FIQR, Revised Fibromyalgia Impact Questionnaire.

Baseline parameters	Intervention group (n=5) (mean ± SD)
Age	56.6 ± 7.7
BMI	28.6 ± 8.3
BPI	6.1 ± 1.3
FIQR tot	54.3 ± 14.3

5.2.3 Experimental design

Participants underwent a 12-week supervised sensorimotor training intervention, attending two sessions per week (approximately 60 minutes each), for a total of 22 sessions. Outcome measures were assessed before (T0) and after (T1) the intervention period. All assessments were conducted between 8:00 and 10:00 am to control for potential circadian rhythm effects. As this was a pilot study, results are reported for the first five participants enrolled (IG = 5).

Intervention Protocol

The intervention consisted of a 12-week sensorimotor training program (2×/week, ~60 minutes/session), combining coordination, stabilization, and multi-joint strengthening exercises, with a focus on proprioception, breathing, stretching, and myofascial release. Sessions, supervised by two kinesiologists specialized in Adapted Physical Activity, followed a gradual progression from basic to complex motor patterns, adapted to each participant. Exercises, inspired by Pilates, yoga, dance, and tai chi, were performed in various positions (standing, seated, lying) using mats, chairs, and sticks. Each session began with a 15-minute warm-up emphasizing breathing, joint mobility, foot proprioception, and neuromuscular activation. An example session is provided in Table 2.

Table 2. Example of a Sensorimotor Training Session for Fibromyalgia

Warm up 15' Activation of the whole system and joint mobilization in standing and seated positions. Focus on the feet, plantar support, and breathing.	• Exercises performed seated, supine, and standing • Plantar self-massage • Gait variations (e.g., forefoot walking, heel walking, foot rolling, with arm swing, arm push, trunk flexion/extension/rotation) • Diaphragmatic and thoracic-lateral breathing exercises (in standing, supine, side-lying, and "rest position") • Joint mobilization with particular attention to the cervical and thoracic spine (e.g., lateral twists, head nods, crunches) • Pelvic mobilization (Gyrokinesis and Pilates methods: anterior/posterior tilt,

	bridging, hip work and variations) • Trunk mobilization: side bending (arch and curling), flexion and rotation, circular and spiral movements (spinal rotation, cat stretch, spine stretch with arms, C curve, mermaid, back extension, quadruped stabilization)
Parte centrale 40' Strengthening of upper and lower limbs with emphasis on the core and pelvic floor. • Mainly isometric exercises • Work load: 8–12 reps x 2–3 sets • Recovery time: 45–60 seconds • Some exercises performed in pairs • Progressive overload principle applied	• Shoulder bridge and variations • Push-ups and variations • Squats (with chair, against wall bars, and variations) • Lunges (with variations) • Isometric exercises in various positions (supine, prone, side-lying) • Balance: single-leg elevation on various planes, relevé
Cool-down 5' Processing proprioceptive input achieved during the session. Improve flexibility, promote relaxation, and enhance self-perception and emotional stimulation.	• Active/passive static stretching • Expressive movement experiences (individual, in pairs, in groups) – Mirror work – Trust exercises – Dance – "Blindfolded" explorations

5.2.4 Intervention assessments

Perceptual measures

Participants completed a battery of validated questionnaires to evaluate pain, symptom burden, sleep quality, psychological factors, and perceived health status: Brief Pain Inventory (BPI) was used to identify pain location, severity and the degree of which pain interferes with daily activities [14]; Revised Fibromyalgia Impact Questionnaire (FIQR) was used to assess the impact of fibromyalgia symptoms over the previous 7 days [15]; Pittsburgh Sleep Quality Index (PSQI) was administered to evaluate sleep quality and disturbances over a 1-month period [16]; Tampa Scale for Kinesiophobia (TSK) was used to assess fear of movement and re-injury in individuals with chronic musculoskeletal pain [17]; and the 36-Item Short Form Survey (SF-36) measured self-reported health across eight domains, including physical, emotional, and social functioning [18].

Functional test

Given the lack of consensus on fitness assessment in FM, a set of widely used tests in rheumatologic research was selected to evaluate physical function, flexibility, and balance. Each test was repeated three times, with the best performance recorded. The following tests were administered in sequence: Handgrip Test [19]; 30-Second Sit-to-Stand Test [20]; Single Leg Stance Test using an inertial sensor (Gyko by Microtech); Trunk Rotation Test [21]; Sit and Reach Test [22]; Scratch Test [23]; Step Test.

5.2.5 Statistical analysis

Given the pilot nature of the study and the small sample size (n = 5), all data were analysed using non-parametric methods. Specifically, the Wilcoxon signed-rank test was used to compare pre- and post-intervention measures, as it provides a more robust approach in the context of small samples and does not assume normality. Data are reported as median and interquartile range (Q1–Q3). The significance level was set at $p < 0.05$. The absolute difference between pre- and post-intervention values was calculated for each parameter to provide a more detailed overview of the individual trends. Additionally, for each significant results the effect size using Hedge's g was reported.

All analyses were completed in SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

5.3 Results

5.3.1 Patients

Out of a total of 7 women with FM who initially expressed interest in the sensorimotor exercise programme, 5 participants completed all 12 weeks of training and were included in the statistical analysis. Among the individuals initially interested, one withdrew after completing the baseline assessments due to scheduling incompatibility with work commitments. Another chose not to begin

the programme and did not complete the initial assessments, citing a lack of continued interest in the project.

5.3.2 Adherence

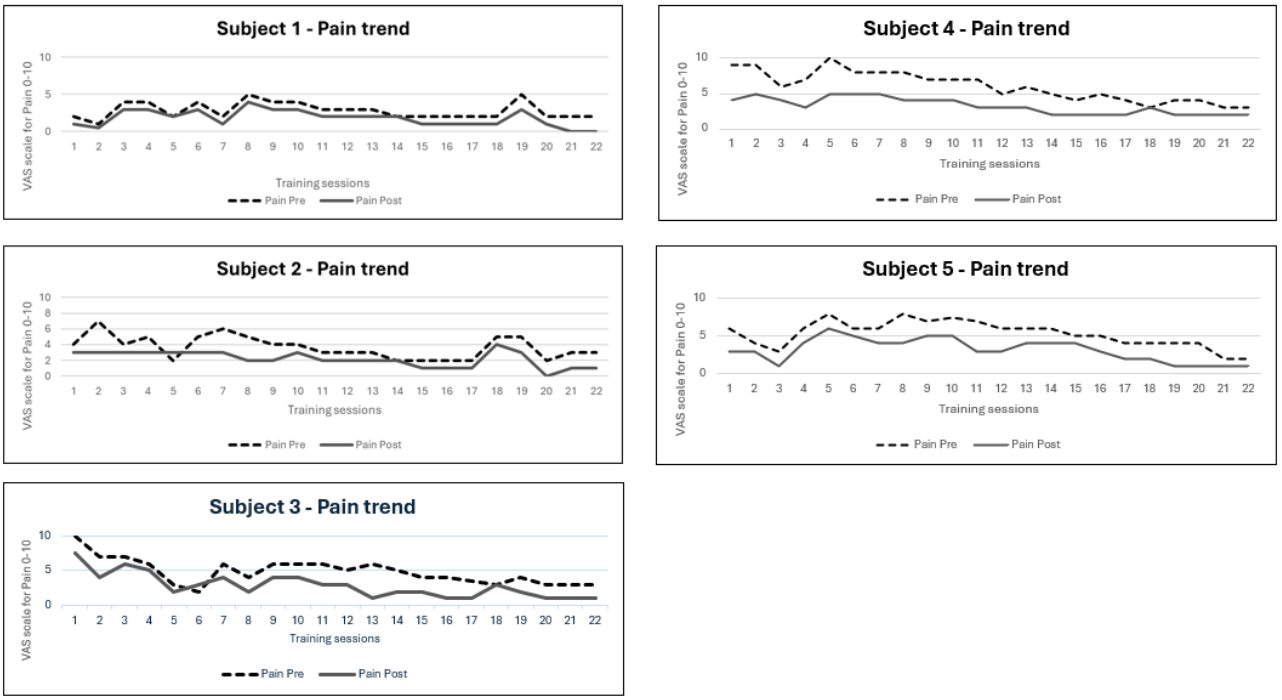
The participants showed complete adherence to the training programme, with a participation rate of 100% to the 24 training sessions required by the protocol. Due to the small number of participants, the two trainers were able to be extremely helpful with the participants, meeting everyone's needs and adapting the training schedule so that not a single lesson was missed.

5.3.3 Pain

BPI scores showed a significant reduction between pre- and post-intervention (p=0.043), with a mean absolute decrease of -3.2 points, showing a large effect size (Hedges' g = -2.14). This change exceeds the minimal clinically important difference, indicating a clinically meaningful reduction in pain perception. Pre intervention participants showed a median of 5.7 a.u. (Q1-Q3: 4.8 – 7.3), while post intervention the median decrease at 2.8 a.u. (Q1-Q3: 2.2 – 3.7).

In addition, for each participant, the trend of perceived pain before and after each training session over the 12-week was graphically represented and confirmed the decreasing evidenced in the analysis of the whole group. The results are shown in Figure 1.

Figure 1. Pain trend for each subject measured before and after each training session through VAS scale



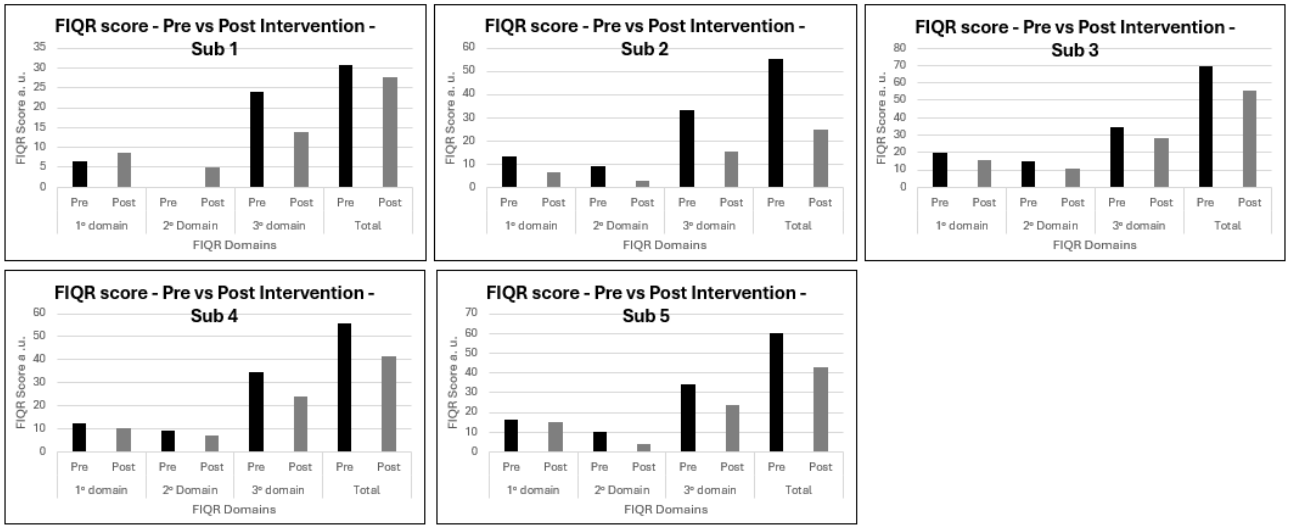
5.3.4 Fibromyalgia symptoms

The scores of the FIQR questionnaire showed statistically significant reductions for the third domain and the total score (both p=0.043), with an absolute mean reduction of -10.8 (pre: median 33.5 a.u., Q1-Q3 28.5 – 34.5; post: median 19.5 a.u., Q1-Q3 14.7 – 26.3, g=-1.93) and -15.9 (pre: median 55.5 a.u., Q1-Q3 43 – 65; post: median 34.4 a.u., Q1-Q3 26.3 – 49, g=-1.26), respectively. These changes exceed the minimal clinically important difference suggesting a clinically meaningful improvement and highlighting a strong effect on symptom burden.

The other two domains did not show significant reductions (1st domain p=0.138; 2nd domain p=0.223) but still exhibited a trend towards reduction of -2.4 (pre: median 12.8 a.u., Q1-Q3 9.4 – 18; post: median 9.3 a.u., Q1-Q3 7.6 – 15.6) and -2.6 (pre: median 9 a.u., Q1-Q3 4.5 – 12.5; post: median 4.5 a.u., Q1-Q3 3.5 – 9), respectively.

In addition, pre and post values of each participant for the three domains and the total score are graphically reported in figure 2.

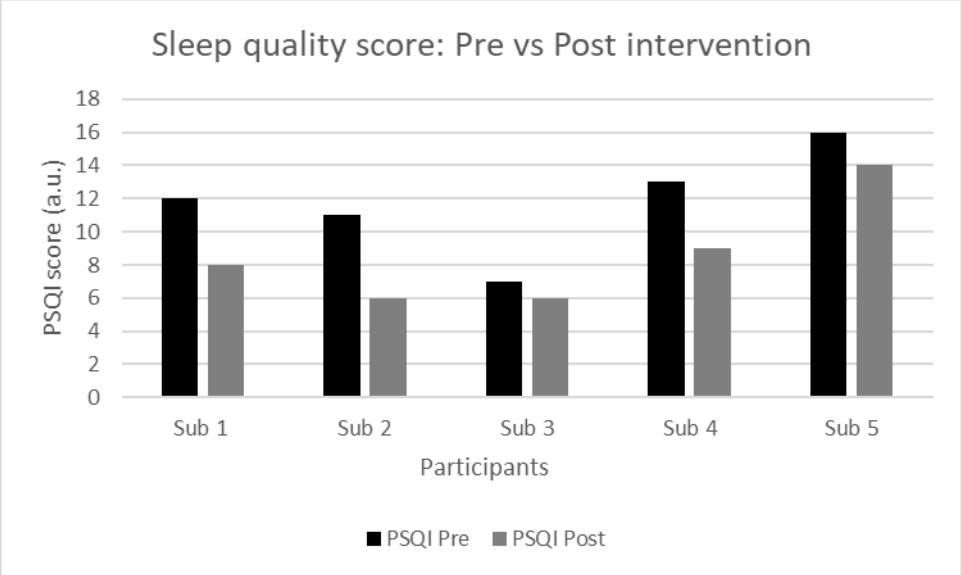
Figure 2. Revised Fibromyalgia Impact Questionnaire score of single domains and total for each participant.



5.3.5 Sleep quality

Sleep quality, assessed through the PSQI, showed a significant reduction with p=0.042 (g= -1.422). Participant showed a median of 12.5 a.u. (Q1-Q3 9 – 14.5) pre intervention, and a median of 8.5 a.u. (Q1-Q3 6 – 11.5) post intervention, with a reduction of -3.2 a.u. in terms of absolute mean, with a meaningful clinical reduction. The score of each participant is showed in figure 3.

Figure 3. Pittsburgh Sleep Quality Index score pre and post intervention of each participant.



5.3.6 Quality of life and kinseiophobia

None of the SF-36 domains showed statistically significant reductions. Median, Q1-Q3, p-value, and absolute mean difference are reported in table 3.

Kinseiophobia level showed no significant difference (p=0.588), still showing a positive trend reduction in the absolute mean difference pre-post of -1.4. (Pre: median 27.5 a.u., Q1-Q3 24 – 34; Post: median 26.5 a.u., Q1-Q3 24 – 31) (Tab.3).

Table 3. The 36-Item Short Form Survey and Tampa Scale of Kinesiofobia results. Median scores for pre- and post-intervention measures across each domain of Tampa Scale for Kinesiofobia and the SF-36 questionnaire, along with the physical health and mental health components, are shown. The data are represented as median values to capture the central tendency, with separate bars for pre- and post-intervention measures.

SF-36 Domains	Pre (median, Q1-Q3)	Post (median, Q1-Q3)	P value	Mean diff. pre-post
Role limitations due to physical health	12 (0 – 25)	37 (0 – 62)	0.157	20

Role limitations due to emotional problems	66 (16 – 100)	66 (16 – 100)	0.564	13.3
Emotional well-being	62 (50 – 76)	66 (60 – 76)	0.465	7.2
General health	42 (25 – 62)	37 (22 – 52)	0.715	-8
Health change	25 (12 – 87)	62 (37 – 100)	0.102	25
Energy/Fatigue	32 (22 – 47)	32 (17 – 42)	0.257	-6
Social functioning	43 (37 – 62)	62 (43 – 75)	0.357	10
Pain	40 (33 – 45)	45 (28 – 67)	0.197	11
Physical functioning	62 (35 – 70)	65 (40 – 80)	0.285	5
Physical component	35 (29 – 45)	44 (29 – 62)	0.109	7
Mental component	47 (38 – 61)	53 (46 – 65)	0.465	6
Tampa Scale of Kinesiophobia	27.5 (24 – 34)	26.5 (24 – 31)	0.588	-1.4

5.3.7 Functional assessments

For the analysis of functional parameters, tests of strength, flexibility and ROM, and static and dynamic balance were analysed. For strength parameters, only 30 sec Sit to Stand test showed a significant increase (+ 4.6 reps, p=0.043, g=1.453). In terms of flexibility and ROM, Sit and Reach test (+ 4.1 cm, p=0.042, g=0.783) and Trunk Rotation Right test (+ 10.8°, p=0.043, g=2.351) showed significant results. Lastly, static balance showed an increase in the right leg, with a decrease in the Ellipse Area (-138.85 mm^2, p=0.043, g=-0.555), while dynamic balance showed an increase in the right leg through the Step test (+2.8 reps, p=0.041, g=1.240). All the results of the functional parameters tests are reported in table 4.

Table 4. Functional parameters results. Median scores for pre- and post-intervention measures are shown. The data are represented as median values to capture the central tendency, with separate bars for pre- and post-intervention measures. Abbreviations: rep, repetitions; kg, kilograms; cm, centimetres; sec, seconds.

Functional parameters	Pre (median, Q1-Q3)	Post (median, Q1-Q3)	P value	Mean diff. pre-post
Sit to Stand (rep)	9 (7 – 11)	14 (12 – 15)	**0.042**	4.6
Handgrip right(kg)	30 (29 – 39)	29 (26 – 39)	0.500	-1.1
Handgrip left(kg)	27 (23 – 38)	26 (25 – 36)	0.500	-0.5
Sit and Reach (cm)	-10 (-13 - -3.2)	-2 (-9.5 – 0.5)	**0.042**	-4.1
Trunk Right (°)	33 (25 – 36)	43 (36 – 46)	**0.043**	10.8
Trunk Left (°)	34 (29 – 37)	42 (32 – 56)	0.138	10.9
Scratch Right (cm)	33.5 (24 – 39)	27.5 (22 – 34)	0.109	-3.8
Scratch Left (cm)	41.5 (36 – 43)	34 (31 – 39)	**0.043**	-4.6
Single leg stand right (sec)	30 (30 – 30)	30 (30 – 30)	1.000	0
Single leg stand left (sec)	24 (15 – 30)	27.5 (25 – 30)	0.180	4
Ellipse area right (cm^2)	78.3 (17 – 317)	21 (7.4 – 37)	**0.043**	-138
Ellipse area left (cm^2)	28 (11 – 113)	34 (15 – 85)	0.893	-7.25
Step right (rep)	7.5 (7 – 9)	11 (9 – 12.5)	0.059	2.8
Step left (rep)	7 (7 – 9)	11 (9.5 – 13)	**0.041**	3.6

5.4 Discussion

The results of this pilot study suggest that a 12-week sensorimotor training program may provide significant benefits for women with FM, particularly in terms of pain perception, overall symptom burden, and sleep quality. Although the sample size was limited (n=5), the data consistently revealed improvements in both symptoms and functional outcomes with large effect size reflecting clinically important difference, supporting the hypothesis that an approach focused on motor control and body awareness may represent a valid and complementary therapeutic option to current EULAR recommendations.

Pain perception, the study's primary outcome, showed a statistically significant reduction both in the pre-post intervention comparison and in intra-session trends. This reduction, consistently observed in all participants, highlights the beneficial effects of adapted physical exercise. Given the nature of pain in fibromyalgia, this result may suggest improved pain regulation. Specifically, it is plausible that high-proprioceptive sensorimotor activities enhance pain regulation, as they may engage central pain control mechanisms more effectively.

The decrease in FIQR scores further confirms a global improvement in symptom management, with positive effects not only on pain but also on daily life impact.

The improvement in Pittsburgh Sleep Quality Index scores represents another relevant outcome, given the centrality of sleep disturbances in FM. This change may be attributed to the combined effects of low-impact exercises, breathing regulation, and relaxation strategies, which are known to benefit circadian regulation and autonomic tone.

Although no significant improvements were found in the SF-36 domains, a general trend toward enhancement, particularly in the physical component, was observed, in line with previous studies [24, 25]. A longer intervention duration or larger sample size may be required to detect more pronounced changes. Similarly, kinesiophobia showed a non-significant yet positive trend, suggesting a reduction in movement-related fear as participants gained confidence throughout the training. This is particularly relevant for women with FM, for whom pain-related fear may lead to avoidance behaviours and physical deconditioning [26,27].

The improvements in physical performances further validate the efficacy of the training program, extending beyond pain modulation to encompass broader functional enhancement. This is consistent with emerging literature supporting somatosensory-based approaches and awareness-focused training methods (e.g., yoga, tai chi, Pilates) in the treatment of FM [24,28,29].

Importantly, FM is a multifactorial syndrome characterized by a complex and heterogeneous symptom presentation, which varies greatly across individuals. This variability reinforces the importance of adopting multidimensional and holistic interventions. Sensorimotor and neuromuscular training, which combines movement quality, body awareness, and functional re-education, may offer an effective strategy to address the full spectrum of symptoms in FM. By integrating both physical and perceptual components, this type of intervention can promote not only symptom reduction but also greater patient engagement and a sense of empowerment in managing their condition.

Furthermore, given its emphasis on postural control, coordination, and psycho-physical well-being, this training modality should be systematically compared with other exercise approaches, such as strength or aerobic training, which are more commonly studied in FM literature [25, 30]. These comparisons would help clarify the specific and potentially complementary benefits of each modality, enabling more personalized and effective treatment planning based on patient needs and preferences.

Another noteworthy finding of this study is the exceptionally high adherence to the training protocol. All participants (100%) completed the 12-week programme without dropping out, with a session attendance rate of over 90%. This level of adherence is particularly striking when compared to previous studies on physical activity in FM sufferers, where drop-out rates are often between 20% and 50%, largely due to exacerbation of pain, fatigue or motivational decline [31,32]. The structured but adaptable nature of sensorimotor training, combined with the focus on gentle, body-conscious movement and psychophysical integration, may have contributed to a greater sense of safety, commitment and perceived benefit among participants. The low-impact format, emphasis on proprioceptive feedback and progressive individualisation probably increased participants' confidence and reduced fear of worsening symptoms. The high adherence not only reinforces the feasibility and acceptability of this approach, but also underscores its potential for real-world application, where long-term commitment is key to achieving lasting benefits. These findings support the inclusion of sensorimotor strategies in FM rehabilitation, not only for their clinical effects but also for their ability to promote adherence, an essential but often overlooked aspect of treatment success.

However, the study has several limitations. The small sample size and lack of a control group limit the generalizability of the findings and preclude definitive causal inferences. Nonetheless, as a pilot study, these results offer a valuable basis for future research, demonstrating both the feasibility and acceptability of the proposed protocol. In addition, the large effect size for of the results, with differences that exceeded the minimal clinically important difference, suggesting a clinically meaningful improvement and highlighting a strong effect on symptom burden.

Interindividual variability in symptom expression and exercise response in FM also represents a potential limitation, suggesting the need for more tailored interventions. Furthermore, the 12-week duration might not be sufficient to modify more stable psychological constructs such as quality of life and kinesiophobia.

In light of these results, future research should focus on randomized controlled trials with larger samples and long-term follow-up.

5.5 Conclusion

This 12-week pilot study indicates that sensorimotor training is a promising non-pharmacological approach for women with fibromyalgia, with potential benefits in reducing pain, improving sleep quality, and enhancing physical function. By promoting motor control and body awareness, this type of intervention may also contribute to improved quality of life. While further research is needed to confirm these findings, the results support the integration of sensorimotor training into clinical practice as part of a multidisciplinary, patient-centred management strategy in line with current EULAR recommendations.

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Declaration of generative AI in scientific writing Authors do not use generative artificial intelligence (AI) and AI-assisted technologies in the writing process.

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CHAPTER 6

General discussion and conclusion

"Integrated General Discussion: Mechanisms and Clinical Implications of Sensorimotor Training"

The following section integrates the findings from the different studies conducted during this PhD program, providing an overall interpretation and contextualization of the main results.

6.1 Overview and Purpose

This doctoral thesis aimed to investigate the effects of sensorimotor exercise on pain modulation and functional performance, in individuals with chronic musculoskeletal conditions, focusing on osteoarthritis (OA) and fibromyalgia (FM). Moreover, modulation in biological markers of inflammation and oxidative stress were analysed. While these disorders differ in aetiology and pathophysiology, both are characterized by chronic pain, altered central pain modulation, and a dysregulated inflammatory/oxidative balance [1][2].

The overarching aim was to explore whether qualitative aspects of movement - such as body awareness, proprioceptive engagement, and breathing integration - could influence both clinical and systemic responses to physical exercise. The work followed a logical progression: to ensure the novelty of experimental work in this thesis, an initial systematic review and meta-analysis were conducted to identify gaps in the existing literature regarding the effects of specific exercise protocols on pain, function and biomarkers in OA. Building on this findings, subsequent interventional studies focused on sensorimotor training, a relatively underexplored yet promising approach, particularly for pain management, aimed to address both clinical and mechanistic questions. In fact, based on the assumption that sensorimotor training may be the most effective form of exercise for pain modulation, improving functional abilities and quality of life, the rationale behind this thesis was to investigate two different sensorimotor exercise modalities whether its analgesic effects could be primarily attributed to biomechanical components of posture and movement, or rather to changes in inflammatory and redox balance. The promising results of this project, particularly with regard to pain, function and adherence, collectively contribute to the understanding of exercise as a multidimensional therapeutic strategy that acts at the biomechanical, neurophysiological and psychosocial levels[3][4].

6.2 Integrated Summary of Findings

The systematic review and meta-analysis (Chapter 2) confirmed that structured exercise interventions consistently improve pain and functional outcomes in individuals with knee OA, in line with previous literature [5][6]. Among the various modalities, sensorimotor and neuromuscular training showed the largest pooled effect sizes, suggesting that interventions targeting proprioceptive control and dynamic joint stability may produce superior analgesic and functional benefits. However, evidence regarding systemic biomarkers of inflammation remained limited, underscoring the need for mechanistic studies [7][8].

Building on this evidence, the interventional studies (Chapters 3–5) provided novel insights into the functional and biological adaptations induced by sensorimotor training. The comparative study between Gyrokinesis and Pilates (Chapter 3) demonstrated that both programs improved pain and performance, but Gyrokinesis led to significantly greater gains in pain reduction, balance, and mobility. This superiority may relate to the dynamic, fluid, and rhythmic nature of Gyrokinesis, emphasizing continuous movement coordination and conscious breathing, as opposed to the more static, core-centred contractions typical of Pilates [9] [10] [11].

Despite the data are limited, according to the biomarker exploratory analysis (Chapter 4), subjects performing Gyrokinesis reported an enhanced antioxidant capacity (increased tGSH and GSH/GSSG ratio) and reduced cellular damage (CK, LDH), while Pilates showed an opposite trend. However, it should be acknowledged that the limited number of participants in this study meant that we were likely underpowered to detect changes in many of these blood markers. Nevertheless, both groups showed a modest increase in IL-1β and TNF-α. Rather than representing a physiological adaptation to exercise, this pattern might reflect the natural progression of the disease, suggesting that physical exercise acts as a protective factor by mitigating, rather than provoking, inflammatory processes [12][13][14]. The more balanced biochemical profile in the Gyrokinesis group supports the hypothesis that the quality of movement patterns, through vagal activation and improved autonomic regulation, may favour a controlled inflammatory response and better redox homeostasis [15] [16].

Finally, the pilot study on women with FM (Chapter 5) showed clinically meaningful improvements in pain, symptom severity, functional limitations, and sleep quality after 12 weeks of sensorimotor training. Although the sample was small, the trend in results, together with an exceptional adherence rate (>90%), highlights both the acceptability and feasibility of this approach in a population traditionally prone to exercise intolerance [17][18]. These findings further support the concept that a light to moderate, gentle and awareness-based exercise can effectively target the multifactorial symptomatology of FM by enhancing central pain modulation, reducing kinesiophobia, and improving overall self-efficacy [19][20][21].

6.3 Integrative Discussion: Mechanisms of Exercise-Induced Pain Modulation

Taken together, the results of this thesis point to a coherent mechanistic framework in which sensorimotor training modulates pain and function through the integration of neuromechanical, psychosocial, and biological mechanisms. At the neuromuscular level, both OA and FM participants benefited from improved movement control and proprioceptive integration. Sensorimotor training encourages joint stabilization through coordinated recruitment of deep stabilizers and improved

alignment, reducing abnormal joint loading and muscle co-contraction patterns associated with pain and stiffness [5][22][23]. The observed improvements in balance and mobility are consistent with enhanced central sensorimotor integration, supporting the suggesting that proprioceptive stimulation contributes to pain inhibition via spinal and supraspinal mechanisms [3][4].

At the psychosocial level, sensorimotor exercise emphasizes awareness, self-regulation, and non-competitive practice. The reduction in pain-related fear, improved sleep quality, and high adherence observed in the FM study illustrate how qualitative, mindful movement fosters a sense of safety and agency [20][19][21]. This aligns with the biopsychosocial model of chronic pain [4], wherein exercise acts not only as a mechanical stimulus but also as a cognitive-emotional intervention capable of restoring body-mind coherence and reducing central sensitization [3][17].

At the biological level, improvements in antioxidant defence, as measured by an increase in tGSH, and modulation of pro-inflammatory cytokines (IL-1β, TNF-α) suggest that exercise exerts anti-inflammatory and antioxidant effects beyond local musculoskeletal adaptations [12][16]. The dynamic movements, rhythmic breathing, and smooth motion patterns typical of Gyrokinesis likely promote parasympathetic activation, which modulates inflammatory signalling via the cholinergic anti-inflammatory pathway [8][15]. These effects may contribute to the attenuation of peripheral sensitization and maintenance of redox balance, factors crucial for pain modulation in OA and other chronic pain syndromes [24][25], thus paving the way for further research and application.

6.4 Common Themes and Comparative Insights

A key theme emerging from all studies is that the *qualitative dimension of movement*, including its rhythm, fluidity, and perceptual richness, is as critical to therapeutic effectiveness as its quantitative aspects, such as intensity or volume.

The Gyrokinesis method embodies a multidimensional approach in which proprioception, breathing, and flow are inseparable components. Such qualitative aspects may explain the superior clinical outcomes observed compared to more conventional exercise forms [8][16][26]. Furthermore, both OA and FM populations, despite their pathophysiological differences, appear to benefit from interventions that restore sensorimotor coherence and autonomic regulation. This convergence supports the view of chronic pain as a systemic disorder of regulation rather than a purely structural problem [3][4]. Sensorimotor training, therefore, represents a promising therapeutic link between body and brain, capable of restoring maladaptive physiological and perceptual processes [22][23].

6.5 Clinical and Theoretical Implications

These findings contribute to redefining exercise as a multimodal systemic therapy rather than a purely mechanical or metabolic intervention. Incorporating sensorimotor elements into rehabilitation may enhance the effectiveness of exercise prescriptions for chronic musculoskeletal pain by targeting both peripheral and central mechanisms of modulation [4][5][6]. Clinically, this approach aligns with EULAR recommendations emphasizing individualized, low-impact, and body-conscious exercise programs [27]. Furthermore, integrating movement practices that emphasise movement quality, such as Gyrokinesis, into standard adaptive exercise protocols could enrich the current exercise therapy paradigm, promoting not only symptom relief but also improvements in self-perception and adherence, two crucial determinants of long-term outcomes[18][19][21].

6.6 Limitations and Future Directions

While the overall findings are consistent and promising, several methodological limitations must be acknowledged. The studies involved relatively small samples and non-randomized allocation, which may limit statistical power and generalizability. Biomarker analyses were exploratory and should be replicated with larger cohorts and broader panels of inflammatory and oxidative markers. Furthermore, the predominance of female participants limits extrapolation to mixed or male populations[17][18]. However, it should also be recognized that these studies focused on clinical populations for whom innovative, body-conscious exercise approaches are particularly needed to enhance pain management and functional recovery. An important strength of this work lies in its use of real-world clinical settings and populations that can most benefit from such interventions. Moreover, the relatively long duration of the training programs compared to similar trials, up to six months, allowed for the assessment of true physiological adaptations and sustainable health benefits, rather than short-term effects observed after only a few weeks of training. The exceptionally high adherence rates further support the feasibility of integrating sensorimotor training into participants' lifestyles.

Future research should pursue randomized controlled trials combining clinical, biological, and psychophysiological measures to elucidate the multidimensional pathways of pain modulation. Additionally, the application of sensorimotor training could be explored in rehabilitation contexts beyond chronic pain, for instance, during recovery after surgery, prolonged bed rest, or neurological events such as stroke, where restoring proprioception, balance, and body awareness may be particularly valuable. The integration of wearable technologies and digital movement analysis could also facilitate the quantification of movement quality and autonomic responses, supporting the development of precision exercise medicine tailored to individual phenotypes of chronic pain [4][15].

6.7 General Conclusions

In conclusion, the collective evidence from this thesis supports the hypothesis that sensorimotor exercise is an effective and biologically plausible intervention for chronic musculoskeletal pain conditions such as OA and FM. Its benefits extend beyond symptom relief, encompassing systemic adaptations in inflammation, oxidative balance, and autonomic regulation. By emphasizing the *how* rather than merely the *how much* of movement, sensorimotor training offers a holistic therapeutic approach consistent with modern integrative models of health [3][4]. These findings encourage the incorporation of proprioceptive, rhythmic, and breath-centred exercise modalities into rehabilitation and clinical practice, fostering a shift from a purely quantitative to a qualitative paradigm of therapeutic movement [15][27].

6.8 References

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CHAPTER 7

“Abroad experience and supplementary research activities”

7.1 “Concurrent multi-organ responses to CHronic physical Activity and INactivity intervention, to increase research discovery in human health and wellbeing” CHAIN STUDY – University of Nottingham

As part of my doctoral studies, between October 2024 and March 2025, and subsequently between September and October 2025, I carried out a research period at the David Greenfield Human Physiology Unit, School of Life Sciences, Medical School, University of Nottingham (UK) as a *visiting PhD student* within the CHAIN Study (*Concurrent multi-organ responses to CHronic physical Activity and INactivity intervention*), coordinated by Prof. Paul L. Greenhaff.

The project aimed to investigate the physiological and metabolic responses occurring during a six-month intervention of either physical activity or inactivity in middle-aged adults at risk of functional decline. To achieve this, the study adopted an integrated, multi-organ approach, employing advanced in vivo methodologies.

During my stay, I was able to acquire and apply a range of techniques, including:

- Stable isotope tracer techniques to measure muscle protein synthesis and whole-body metabolic turnover;
- Metabolic and functional monitoring through oral glucose tolerance tests with indirect calorimetry, continuous glucose monitoring systems, postural accelerometers and heart rate monitors;
- Cardiorespiratory fitness testing (VO_2max), computerised isokinetic dynamometer (Cybex);
- Ultrasound techniques for musculoskeletal and vascular investigations;
- Magnetic Resonance Imaging (MRI) to assess body composition, muscle and adipose tissue volumes, as well as the morphology of organs such as the heart and brain;
- Magnetic Resonance Spectroscopy (MRS) to analyse intra-muscular and hepatic lipid content and to study post-exercise phosphocreatine resynthesis kinetics;
- ‘Omics’ and molecular analyses on biological samples, aimed at characterising metabolic profiles and gene expression patterns related to metabolism and inflammatory processes.

Beyond the acquisition of technical skills, I was actively involved in data collection, working within a multidisciplinary team of physiologists, biochemists, clinicians, and laboratory technicians. This experience allowed me to gain an integrated perspective on the adaptive responses to physical activity, while strengthening my methodological and analytical competencies.

Overall, this research stay represented a significant contribution to my doctoral training, providing both conceptual and practical tools that informed the elaboration and interpretation of the results presented in this thesis.

7.2 EpiAF - Physical activity and epigenetic modulations in breast cancer: a comparison between combined training, dance therapy and usual care

As part of my supplementary research experience, I actively participated in the project entitled *"EpiAF - Physical activity and epigenetic modulations in breast cancer: a comparison between combined training, dance therapy and usual care."*

Specifically, I contributed to the data collection phase, performing post-intervention assessments of the participants. My role included conducting the functional evaluations at the end of the training period, such as the 6-minute walking test, grip strength test, 30-second sit-to-stand test, balance and flexibility assessments (Tandem test, sit-and-reach, back scratch, and trunk rotation), as well as supporting the administration of psychological questionnaires (EORTC QLQ-C30, HADS, FA-12, and PSQI).

Through this experience, I acquired practical skills in standardized testing procedures, data handling, and interaction with clinical populations, enhancing my understanding of research methodology in the field of exercise oncology and the multidisciplinary evaluation of cancer rehabilitation outcomes.

7.3 New treatment strategies to counteract the onset and progression of uremic sarcopenia in patients with chronic kidney disease (CKD)

As part of my supplementary research experience, I took part in the project entitled *"New treatment strategies to counteract the onset and progression of uremic sarcopenia in patients with chronic kidney disease (CKD)."*

The main aim of the study was to evaluate the potential synergistic effects of a targeted physical exercise program combined with a personalized dietary-nutritional therapy and the daily intake of functional antioxidant and anti-inflammatory bars on the prevention and progression of uremic sarcopenia in patients with CKD under conservative therapy.

Within this project, I was directly involved in the exercise intervention phase, training several patients throughout the entire experimental period (3 months). Specifically, I supervised and guided the participants assigned to the exercise groups in performing the home-based training sessions (three

times per week, approximately one hour per session), ensuring correct execution, adherence, and safety. The exercise protocol included aerobic, resistance, and flexibility components tailored to each patient's clinical condition and physical capacity (see Table 1).

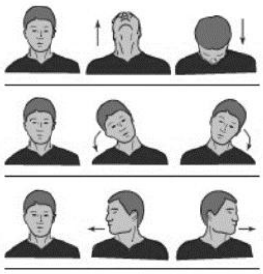
This experience allowed me to develop practical expertise in exercise prescription and supervision in clinical populations, deepen my understanding of the interaction between physical activity and chronic kidney disease, and strengthen my research and clinical skills in the context of exercise physiology and rehabilitation.

Table 1. Representative exercise protocol sheet used in the study

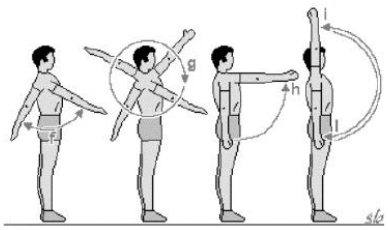
PROTOCOLLO DI ESERCIZI: Combined Training with Resistance Band

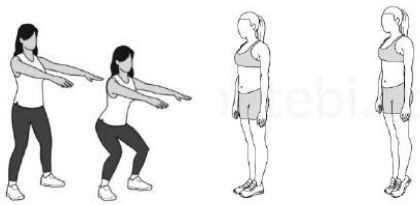
RISCALDAMENTO: 15 minuti

Mobilità articolare del collo	
Esercizio	**Ripetizioni**
Flesso-estensioni	8
Recupero	10s
Latero-flessioni	8
Recupero	10s
Mezze Circonduzioni + Mezze circonduzioni combinate con contrazione delle spalle	4+4

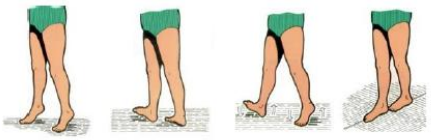


Mobilità articolare per gli arti superiori a corpo libero	
Esercizio	**Ripetizioni**
Circonduzioni delle spalle per dietro	10
Circonduzioni delle spalle per dietro alternate dx e sn	10+10
Circonduzioni delle spalle per avanti	10
Circonduzioni delle spalle per avanti alternate dx e sn	10+10
Recupero	20s
Circonduzioni per avanti-alto verso dietro alternate dx e sn combinate con calf raises e mezzo squat	10+10
Circonduzioni per dietro-alto verso avanti alternate dx e sn combinate con calf raises e mezzo squat	10+10
Recupero	20s
Circonduzioni per avanti-alto verso dietro combinate alla torsione del tronco dx e sn	10+10





Parte Funzionale	
Esercizio	**Ripetizioni**
Camminare sugli avampiedi ginocchia tese	10+10
Camminare sui talloni ginocchia tese	10+10
Camminare con rullata del piede	10+10
Camminare Tandem	10+10
Equilibrio monopodalico Y-Balance dx e sx	2+2
Equilibrio monopodalico con cuscino tra le ginocchia dx e sx	20s+20s



ESERCIZI DI FORZA: 20 minuti


CIRCUITO 1

Esercizio	Ripetizioni
Squat	10
Chest Press	10
Reverse Sit up	10
Lounges	10
Shoulder Press	10
Recupero	1min




CIRCUITO 2

Esercizio	Ripetizioni
Biceps Curl	10
Quadriceps	10
Bridge	10
Hamstring	10
Row	10
Recupero	1min






CIRCUITO 3

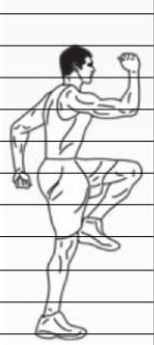
Esercizio	Ripetizioni
Overhead Squat	10
Lounges + Biceps Curl	5dx+5sn
Leg press 45°	10
Bridge Single Leg	10dx+10sx
Stacco+ Row	10
Recupero	1min





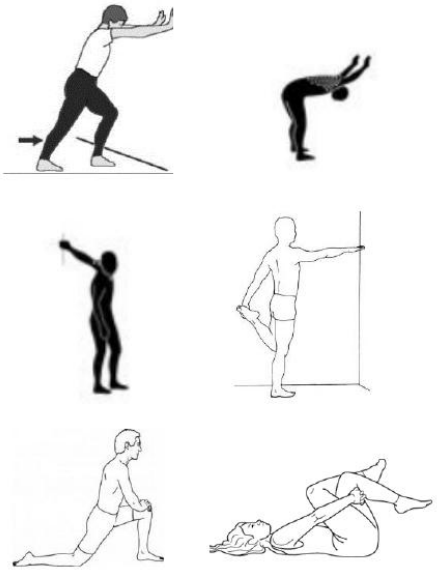

PARTE AEROBICA 1: 15 minuti in musica

Parte Aerobica	
Tipologia di Passo	**Tempi**
Lounges aleternati dx e sn	8
V Step dx	8
Leg Curl alternati dx e sn	8
Knee Up alternati dx e sn	8
Apro chiudo dx	8
Marcia	8
Kick dx e sn + Pounge sn e dx	8
Lounges alternati sn e dx	8
V Step sn	8
Leg Curl alternati sn e dx	8
Knee Up alternati sn e dx	8
Apro chiudo sn	8
Marcia	8
Kick sn e dx + Pounge dx e sn	8



DEFATICAMENTO: 10 minuti

Defaticamento	
Esercizio	**Ripetizioni**
Allungamento catena cinetica posteriore degli arti inferiori dx avanti e sn avanti	30s+30s
Allungamento lunghissimo del dorso e trapezio	30s
Allungamento gran pettorale e muscoli anteriori di spalla dx e sn	30s+30s
Allungamento quadricipite femorale dx e sn	30s+30s
Allungamento Psoas dx e sn	30s+30s
Allungamento Piriforme dx e sn	30s+30s



CHAPTER 8

“Extra Scientific production”

This chapter aims at presenting the candidate’s scientific publications, contributions to national and international conferences, and professional memberships.

8.1 Publications

The Effect of Exercise-Based Interventions on Health-Related Quality of Life of Patients with Hematological Malignancies: A Systematic Review and Meta-Analysis
Borsati, A. et al (2025). *Healthcare*, *13*(5), 467. https://doi.org/10.3390/healthcare13050467

Effect of prebiotics, probiotics and symbiotics on gut microbiota in sedentary subjects and athletes: narrative review
Grazioli, E. et al (2025) Medicina dello Sport;77(4):480-90

Role of exercise on pain, functional capacity, and inflammatory biomarkers in osteoarthritis: A systematic review and meta-analysis
Mauri, C., et al (2025). *Annals of physical and rehabilitation medicine*, *68*(3), 101909. Advance online publication. https://doi.org/10.1016/j.rehab.2024.101909

Dropout and compliance to physical exercise in menopausal osteopenic women: the European "happy bones" project
Grazioli, E. et al (2023). Frontiers in sports and active living, 5, 1221409

Performing Group-Based Physical Activity (Gbpa) in the Work-Place: Survey and Sociological Considerations of the "Happy Bones" Project
Lenzi, F.R. et al (2023) Sustainability, 15, 480. https://doi.org/10.3390/su15010480

Osteoporosis prevention in the workplace: the "Happy Bones" protocol
Moretti, E. et al (2023) Medicina dello sport 76(2)

Phytonutrients and weight control: the role of polyphenols
Parisi, A. et al (2023) Medicina dello Sport;76(1):6-31

The Preventive Role of Physical Activity in Systemic Sclerosis: A Cross-Sectional Study on the Correlation with Clinical Parameters and Disease Progression
Antinozzi, C. et al (2022) Int journal of environmental research and public health, 19(16),10303

8.2 Conferences and Seminars

XVI National Congress SISMES – Società Italiana delle Scienze Motorie e Sportive

"Feasibility and Preliminary Effects of a 12-Week Sensorimotor Training Program in Women with Fibromyalgia: A Proof-of-Concept Pilot Study"
Parma, 06/11/2025 – 08/11/2025
SHORT COMMUNICATION

ECSS - European College of Sport Science Congress 2025
"Gyrokinesis® reduces pain and results in greater improvements in postural sway when compared to Pilates in individuals with osteoarthritis: a 24-week pilot study"
Rimini, 01/07/2023 – 04/07/2023
ORAL PRESENTATION

XV National Congress SISMES – Società Italiana delle Scienze Motorie e Sportive

"Sensorimotor training in osteoarthritis: role of the Gyrokinesis® and Pilates method on pain and functional limitations"

Chieti, 19/09/2024 – 21/09/2024
POSTER TEASER

ECSS - European College of Sport Science Congress 2024
"Effects of a 12-week Gyrokinesis® training on OA-related pain and functional abilities"
Glasgow, 02/07/2023 – 05/07/2023
ORAL PRESENTATION

Congresso "Reumatologia oggi e domani - Focus on: temi reumatologici di pratica clinica"
Responsabile scientifico: dott.ssa Donatella Fiore, Responsabile UOSD Reumatologia ASL Roma 1
"Effects of a 24-week Gyrokinesis® training on OA-related pain, functional abilities and inflammatory biomarkers: preliminary results" 13/04/2024
INVITED SPEAKER

Webinar "Curiamo con la ricerca" – Physical activity and osteoarthrosis
University of Perugia, 09/04/2024

ORAL PRESENTATION

XIV National Congress SISMES - "Can Animal Assisted Interventions counteract apathy and improve Physical Activity levels in psychiatric patients with cognitive disability? A Case Study"
Naples, 02/11/2023 – 04/11/2023
POSTER TEASER

XXXVII Congress FMSI - "Promoting physical activity in the workplace: effect on compliance, bone health and functional parameters in post-menopausal women of the Italian Happy Bones pilot action"
Rome, 20/07/2023 – 22/07/2023
POSTER PRESENTATION

ECSS - European College of Sport Science Congress 2023
Paris, 04/07/2023 – 07/07/2023

Webinar "Curiamo con la ricerca" - Happy Bones training protocol
University of Perugia, 30/03/2023
ORAL PRESENTATION

8.3 Professional Memberships

The Physiological Society, Member since 2024

European College of Sport Science, Member since 2023

SISMES – Società Italiana Scienze Motorie e Sportive, Member since 2023

FMSI – Federazione Medico Sportiva Italiana, Member 2023-2024