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Review Article

The Role of Pre-nociceptive Mechanical Factors in the Physiopathology of Musculoskeletal Pain

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Abstract

Musculoskeletal pain represents an important cause of medical care and disabilities worldwide. The pathophysiology of musculoskeletal pain of mechanical origin is divided into 4 phases that include the pathophysiological mechanisms from the activation of the nociceptors to the reception and interpretation of the nociceptive stimulus in the cortical centers. However, there are factors that precede nociceptive activation, which we have called pre-nociceptive mechanical factors. The objective of this manuscript is to establish a theoretical framework on the implications that pre-nociceptive mechanical factors have in the origin and perpetuation, as well as the management of musculoskeletal pain. Mechanical overload and functional alteration of the musculoskeletal system are factors that precede and may favor the activation of the nociceptive cascade. Mechanical overload occurs when the magnitude of the load exceeds the capacity of the musculoskeletal system. Likewise, a dysfunctional musculoskeletal system has a poor adaptive capacity to the mechanical loads it faces and this predisposes it to generate functional compensations; in both cases, tissue overload, micro-structural damage, inflammation, tissue sensitization and tissue degeneration or macro-structural damage may occur in the long term. Both factors must be considered when implementing therapeutic strategies for the prevention and treatment of musculoskeletal pain of mechanical origin.

Keywords: Mechanical overload, Musculoskeletal dysfunction, Musculoskeletal overload, Musculoskeletal pain, Pre-nociceptive factors

Introduction

Musculoskeletal pain is defined as acute or chronic pain that affects bones, joints, muscles, ligaments, tendons and even nerves[1-3]. Musculoskeletal pain can be a relevant symptom that causes some degree of disability in more than 150 established pathological entities[4,5]. Currently, musculoskeletal pain represents a very common health problem and one of the main causes of medical consultation in primary care[2,4,6]. It has been reported that the global prevalence of musculoskeletal pain ranges from 13 to 47%[4] and the incidence of chronic musculoskeletal pain is estimated at 8.4% per year[4]. Musculoskeletal pain generates a great impact on individuals who present it, and it is one of the first 10 causes of disability[2]. Despite the numerous resources allocated to solving this symptom, its prevalence and impact on the population health has not changed much in the last decade and will even tend to increase in many countries[6].

Musculoskeletal pain can have a clinical pattern of traumatic, mechanical, inflammatory or tumor[1]. When nociceptive activation is caused by mechanical stimuli that affect the tissue, it is considered to have a mechanical pattern; additionally, pain is associated with mechanical loading and decreases with rest or light movement[7]. In the pathophysiology of nociceptive pain, 4 phases are described:

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transduction, transmission, modulation and perception[8-10]; these phases include the pathophysiological mechanisms from the activation of the nociceptors to the reception and interpretation of the nociceptive stimulus in the cortical centers[8-11], and involve various pathophysiological phenomena such as the release of inflammatory mediators, sensitization of tissue nociceptors, central sensitization and tissue degeneration, among others, which interact and favor the appearance of pain as well as its transition from the acute to the chronic stage[8-10]. It is important to emphasize that these pathophysiological mechanisms occur after the nociceptive activation.

However, there are factors that precede nociceptive activation and can predispose the onset of musculoskeletal pain. Nevertheless, in the specialized scientific literature on the pathophysiology of musculoskeletal pain, these pre-nociceptive factors are not widely discussed.

The objective of this manuscript is to establish a theoretical framework on the implications that pre-nociceptive factors have in the origin and perpetuation of musculoskeletal pain and their importance in the management of musculoskeletal pain of mechanical origin, from a particular perspective of the Pain Training and Research Team (EFID, for its acronym in Spanish).

Methodology

For the construction of this manuscript, a search was carried out in online databases such as the National Library of Medicine (MEDLINE/PubMed), Web of Science, PEdro, Cochrane Central Register of Controlled Trials (CENTRAL) and Scientific Electronic Library Online (SciELO), for literature published up to november 2024. In addition, other sources, such as Google Scholar were included in the search to identify documents that might be useful but were not included in the databases mentioned above. The search was conducted in two stages, using several search strategies and keywords to include as much information as possible on the topic. The main search included the following terms: *((prenociceptive factors) and (musculoskeletal pain or musculoskeletal injury or musculoskeletal disorders or musculoskeletal disease))*. The secondary search was conducted using combinations of the terms related to pre-nociceptive factors: *((mechanical overload or mechanical load or cumulative load or repetitive load or sustained load or prolonged load) and (musculoskeletal pain or musculoskeletal injury or musculoskeletal disorders or musculoskeletal disease))*, as well as *((musculoskeletal dysfunction or musculoskeletal deconditioning or musculoskeletal overload or musculoskeletal fatigue or tissue overload or tissue fatigue) and (musculoskeletal pain or musculoskeletal injury or musculoskeletal disorders or musculoskeletal disease))*. Additionally a direct search was also conducted using the bibliography referenced in the identified documents to identify documents that could be useful and that were not found in the database. Preclinical studies conducted in vitro or using animal models, clinical studies, reviews or editorials were included, which contained relevant information for the topic. Using the information found, a theoretical framework was integrated, explaining the implications of mechanical prenociceptive factors in the origin and perpetuation of musculoskeletal pain and its treatment.

Results

Definition of pre-nociceptive mechanical factors

Various factors have been associated with the indirect risk of suffering pain in the musculoskeletal system, such as age, sex, cigarette/tobacco, low educational level, sedentary lifestyle, inadequate nutrition, little social interaction, low family income, depression, anxiety and sleep disorders, among others[12,13]; However, none of these factors directly cause musculoskeletal pain, they can increase the susceptibility or vulnerability to develop or perpetuate it. Other factors intervene more directly in the pathophysiology of musculoskeletal pain, such as the mechanical overload and the functional alteration of the osteo-myo-neuro-articular system (OMNAS), which we have called *pre-nociceptive mechanical factors* (PMF) (Figure 1).

The PMF precede and can contribute to the activation of the nociceptive cascade[14-19], and could participate in the origin or perpetuation of musculoskeletal pain of mechanical origin (MPMO). Therefore, its participation could come from 3 situations:

- MPMO due to mechanical overload of the OMNAS.
- MPMO due to functional and/or structural alteration of the OMNAS.
- MPMO due to the combination of both.

Mechanical Overload

The OMNAS is responsible for supporting and handling mechanical loads within a safe range, where regular mechanical loads do not generate overload or tissue damage[14,15]. The *mechanical overload* occurs when the magnitude of the load exceeds the adaptive capacity of musculoskeletal tissue[16], a situation that can occur when the load is very high and/or there is a decrease in the adaptive capacity[14,15].

The various tissues that make up the OMNAS are constantly subjected to mechanical loads of tension, compression and shear that generate mechanical stress in the tissue[17,18], responding in various ways according to the various biomechanical properties of the tissue, such as elasticity, resilience, anisotropy and viscoelasticity[18,19]. The response of the tissue and the possibility of generating damage are directly related to the magnitude and direction of the load[17,18]. From this perspective, when the magnitude of the load is very large and exceeds the adaptive capacity of the tissue, it is possible that a mechanical overload occurs, even if the OMNAS has a normal adaptive capacity[15,16]. However, if the OMNAS has decreased adaptive capacity and is unable to manage the load[16], there is a greater possibility of generating mechanical overload, although the load is moderate or low.

We have classified mechanical overload into 4 categories according to the mechanical load involved.

Type I (Acute Dynamics): It occurs in the context of acute trauma, where the load exceeds the adaptive capacity due to its intensity and an acute mechanical overload of the tissue is then produced[14], abruptly exceeding the fracture point of the stress-deformation curve of the tissue involved, generating sudden macro-structural damage[15,19].

Type II (Chronic Dynamics): In the context of repetitive stress injuries, the load is of variable intensities, but of high volume, frequency and/or low density, generating repetitive deformation of the tissue and altering its biomechanical characteristics, which results in a decreased adaptive capacity, with the consequent progressive accumulation of microstructural damage[14-16,18,20], inflammation and tissue sensitization[18,20,21] and long-term tissue degeneration or structural damage[16,18,20]. The most typical example is an injury due to overuse or overload in athletes, which is also called stress injury[20].

Type III (Chronic Statics): In this case, the static or postural load generates sustained stress-deformation on the connective tissue, especially on the fascia, altering its biomechanical characteristics and decreasing its adaptive capacity, requiring less stress to induce more deformation[14,15,18,19]. Prolonged static loads generate a constant compressive effect (traction and compression)[18], which if excessive, can promote deformation of the connective tissue and the reduction of proteoglycan synthesis, favoring tissue deformation, which can generate diffuse microstructural damage to the extracellular matrix[22-25]. This, in turn, can trigger the release of proinflammatory cytokines and nociceptive activation[22,23]. If the inflammation is prolonged over time, it can lead to sensitization of peripheral nociceptors and decreased proprioceptive function of the affected myofascial tissue[22,23]. This type of load is the one most closely related to OMNAS dysfunction, since diffuse damage to the connective tissue could alter proprioceptive inputs and disrupt motor control, which could predispose the OMNAS to subsequent injuries due to dynamic overload. This is the context of incorrect positions maintained over time[26]; the most obvious example is back pain associated with prolonged sitting in work spaces without adequate ergonomic control[27].

Type IV (Mixed Static and Dynamic Loads): In these cases, sustained postures plus repetitive low intensity dynamic loads are combined, such as those that occur in office work. These types of loads are the most common in repetitive strain injuries[28].

Some types of activities related to an increased load (both static and dynamic) that have been associated with the presence of MPMO are: prolonged periods sitting[29,30], prolonged periods standing[30], activities that involve frequent performance of repetitive movements with the extremities[30,31], activities that involve the frequent mobilization of heavy loads[30,31], jobs that involve the use of machinery that generates whole-body vibration[30], postural alterations in the foot[32], postural alterations in the pelvis[33], discrepancy in the length of lower limbs[32,33], and obesity[13,30].

Functional alteration of the OMNAS

The second factor to evaluate among the causes of mechanical overload is the decrease in the adaptive capacity (dysfunction) of the OMNAS, which represents a decisive factor in the appearance of musculoskeletal pain of mechanical origin (MPMO).

The load applied to the OMNAS is actively absorbed by the myofasciotendinous system (muscles, fascia and tendons) through the eccentric, isometric and concentric actions that seek to absorb and dissipate the imposed load, and passively received by the osteo-articular system (bones, cartilage, ligaments and the capsule-synovial tissue)[15,34]. To manage and adapt to these loads, the OMNAS has different motor capacities[22,34], the most important for musculoskeletal health are strength, mobility, endurance and motor control[35]. These give the OMNAS the ability to efficiently and effectively manage the mechanical and metabolic stress that the loads generate on the system.

The OMNAS in optimal functional and structural conditions manages to handle the applied loads with minimal mechanical stress and the lowest energy expenditure[7,19,24]. However, if the OMNAS has structural or functional alterations, it is more likely that applied loads could generate mechanical overload in the tissue[12].

The presence of structural damage in the OMNAS tissues may lead to inefficient load management stimulating nociceptive activation. Structural damage has been directly associated with the presence of musculoskeletal pain and this has generated a model that establishes a linear relationship between injury - degeneration and pain, however, the relationship between structural tissue damage and clinical manifestation (pain) is not always clear[36]. This is reflected in the lack of correlation between pain and the structural condition evidenced in imaging studies[36]. The current definition of pain by the IASP in 2020 defines pain as "unpleasant sensory and emotional experience, associated with a real or potential injury"[37], giving the possibility that the appearance of pain does not necessarily entail the presence of "real" structural damage, and there could be other "potential" mechanisms associated with the appearance and perpetuation of pain despite the structural integrity of the tissue from which the nociceptive stimulus comes[36]. It is also important to note that the presence of musculoskeletal pain may not be due to the structural alteration of a single tissue, but by the presence of structural alterations in several tissues at the same time[21] or in complex regions with anatomic interdependence[38]. We have called this concept "*trans-structurality of the pain*". The above suggests the

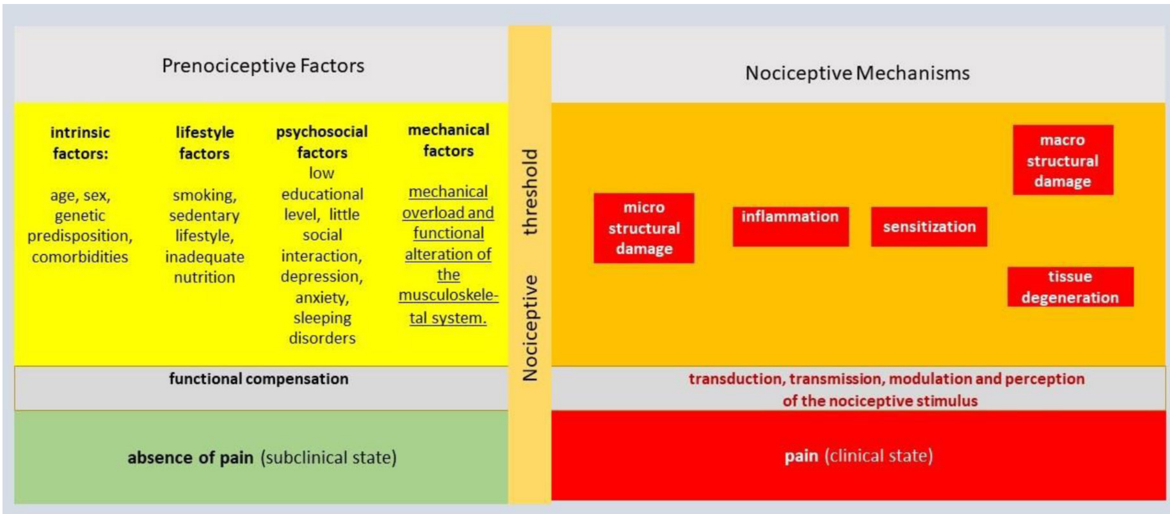

Figure 1. Pre-nociceptive mechanical factors and musculoskeletal pain of mechanical origin.

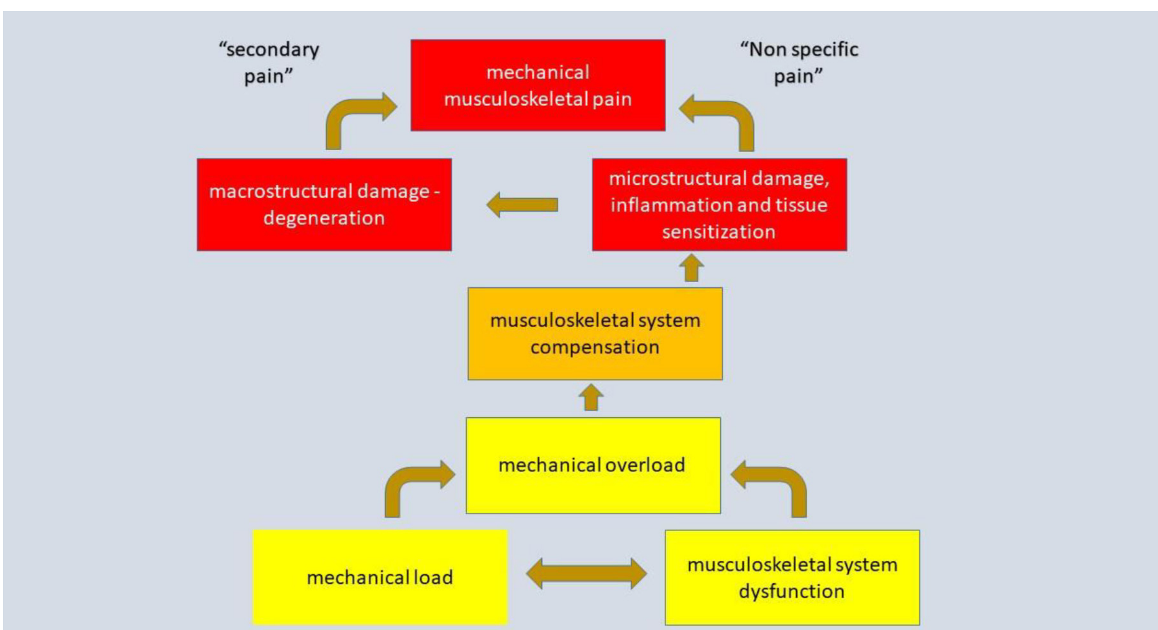

Figure 2. Mechanical loads and dysfunctional musculoskeletal system.

existence of mechanisms other than the structural alteration of the OMNAS that participate in the genesis of MPMO[26,39]. The functional alteration in some elements of the OMNAS may participate in the genesis and perpetuation of pain[30].

If the OMNAS is in functional integrity and faces optimal loads, a progressive adaptation to the loads to which it is subjected occurs, achieving efficient management of energy expenditure and mechanical stress[14,15,19,24].

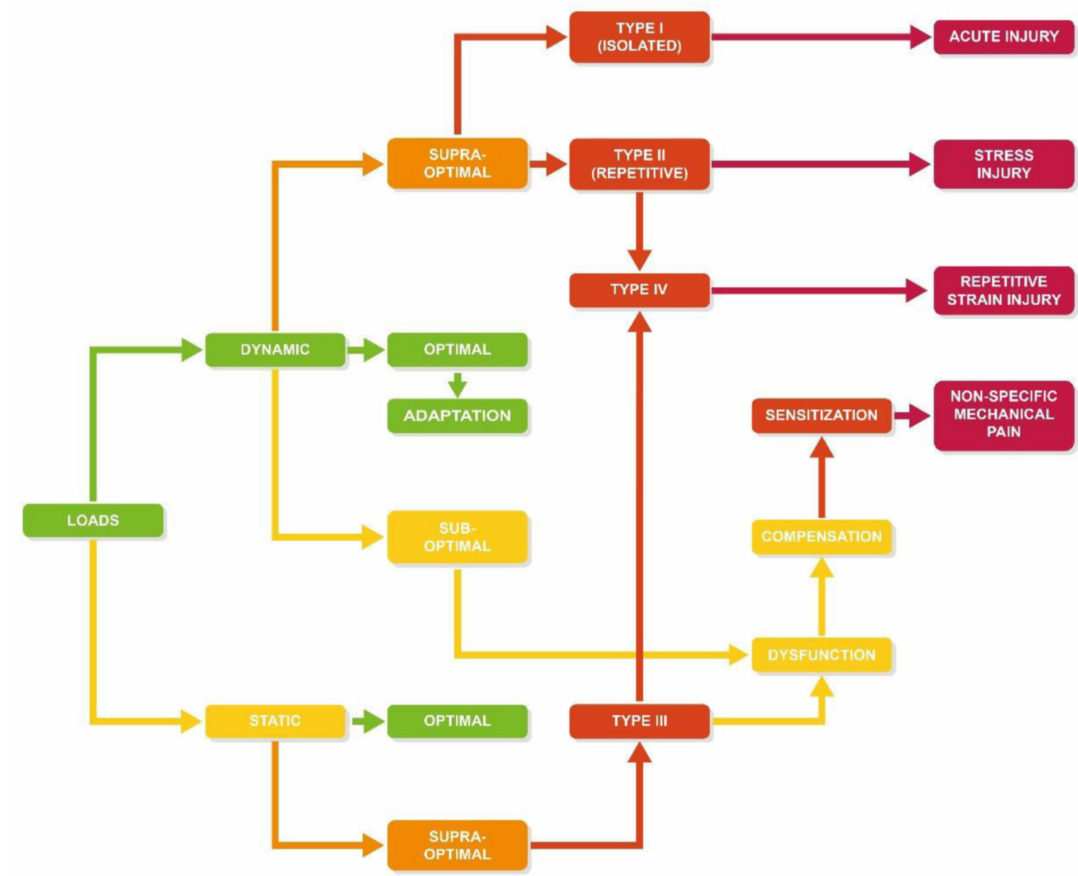

Figure 3. Mechanical loads and musculoskeletal pain.

However, when a tissue of the OMNAS presents functional alterations, the system initially responds through compensation phenomena[40], in which the involved tissues seek to temporarily preserve the functionality of the system, but this may imply greater energy expenditure, greater internal load or greater time invested to perform the same task[14,15,40]. When this is sustained over time, the increased mechanical stress and the inability of the tissue to adapt, generate a state of tissue microstructural damage (localized or diffuse)[15,16,18,20,22], which can lead to the release of proinflammatory cytokines and reactive oxygen species[9,18,20,22,23], and this in turn can promote nociceptive activation and tissue sensitization, with the subsequent appearance of pain[9]. At this point, imaging studies present negative results on many occasions, not finding macrostructural damage that causes pain, which could explain pain of non-specific origin. The chronicity of this condition can favor tissue degeneration and macrostructural damage[18,20,21].

Every component of the OMNAS participate in the main function of this system, the transmission of loads. The mechanisms of management and absorption of loads do not involve a single tissue, but involve muscles, tendons, ligaments, bone, cartilage and sensory system[15]. It is possible that the functional alteration of one of the tissues in the OMNAS, can functionally overload other components. OMNAS has the ability to establish functional relays between tissues, in which the function of a certain tissue is relieved by another tissue that has a different function but can "help" the dysfunctional tissue, this being a compensation mechanism[40].

Among the most frequent functional alterations are muscle weakness[41,42], muscular imbalance between agonists and antagonists[43,44], lower muscular resistance[45], decrease or increase in the normal joint range[46,47], alterations in flexibility[48], alterations in coordination and motor control[44,48], deficits in the sensorimotor system[49,50], among others. These factors associated with the genesis of musculoskeletal pain can also be magnified by the presence of pain itself[51], establishing a vicious circle that favors the chronicification of the condition. The optimal function and structure of the OMNAS is essential for a proper management of the applied loads, generating minimal mechanical stress and low energy expenditure[14].

The interaction between the variants of the load and the OMNAS function is expressed in Figure 2 and the relationship between types of mechanical loading and musculoskeletal pain in the Figure 3.

Discussion

Implications of PMF in the management of musculoskeletal pain

The PMF can contribute to the activation of the nociceptive cascade and the appearance of sensitization and structural injury of the tissues[14,16,19], participating in the genesis and chronification of MPMO[9], so the modification of loads and improvement of the OMNAS functionality may be essential for the prevention and treatment of MPMO. The detection of these factors is essential to develop a multimodal and interdisciplinary plan, that focuses on optimizing the mechanical conditions that lead to the onset and perpetuation of many musculoskeletal symptoms (including pain), and aims to prevent or reduce the activation of the nociceptive cascade[52].

Guidelines for the treatment of musculoskeletal pain describe numerous pharmacological and non-pharmacological tools for the treatment of different conditions in their acute and chronic stages[52-54], however, they do not specify or delve into the control strategies of the pre-nociceptive mechanical factors. The therapeutic ladder proposed for the treatment of chronic musculoskeletal pain[53] and for the treatment of chronic non-cancer pain[54], only describes the pharmacological strategies at each step and only mentions the possibility of adding adjuvants or integrative therapies as an addition to pharmacological treatment, without detailing. The modification of PMF should represent a fundamental element in the prevention and treatment of MPMO.

The therapeutic strategies for the control of pre-nociceptive mechanical factors are detailed below.

Modification of mechanical loads

The first therapeutic strategy to reduce the impact of PMF on the pathophysiology of pain consists of modifying the qualitative and quantitative aspects of mechanical loads, with the aim of changing the magnitude and type of mechanical loads supported by the OMNAS.

Therapeutic strategies focused on load modification have two basic principles:

a) Reduce the exposure time of sustained static loads to avoid excessive deformation of the supporting tissues.

b) Correctly dose the dynamic loads imposed on the OMNAS, to prevent its adaptive capacity from being exceeded, and prevent the compensation, sensitization or injury mechanisms from being generated.

Many of the factors that can generate mechanical overload, such as postural alterations, are immersed in the patient's lifestyle and/or are not clearly identified by the patient or by the physician, which highlights the need to dedicate a special time to the medical evaluation for the identification or addressing of these situations.

Strategies should be implemented that reduce the mechanical load on the OMNAS, such as weight loss[55], use of ergonomic strategies[56,57], postural and joint hygiene[55,58,59], use of stabilizing orthoses in those patients who have instability joint[55,60], use of walking aids in patients in whom pain deteriorates the qualitative and/or quantative aspects of walking[55] and use of plantar orthoses[61-63], always based on a correct evaluation to identify the patient's needs. The implementation of these strategies aims to reduce the mechanical overload on the musculoskeletal tissue and thereby reduce the nociceptive activation that can occur due to inflammation, sensitization and structural damage of the tissue.

Improvement of the OMNAS functionality

Another therapeutic strategy that reduces the impact of PMF on the pathophysiology of pain is the improvement of the functionality of the OMNAS. Through cellular and neural mechanisms, the mechanical stress can induce a variety of metabolic, tissue, morphological and mechanical changes, that lead to functional and structural optimization of the tissue[64,65].

Skeletal muscle tissue has the ability to adapt to loads[64] and increase its functional and structural capacity in the face of increased demands, with the aim of reaching a new point of balance that imposes less stress on the system and therefore less energy expenditure[64,65], which is called the *plastic capacity of skeletal muscle tissue*. This phenomenon represents the basis of the main therapeutic strategy in this step, therapeutic exercise, aimed to increase the adaptive capacity of the OMNAS to external loads thus reducing the risk of mechanical overload, sensitization, injury and pain.

The proper functioning of the neuromuscular system favors the loads applied to the OMNAS to be actively managed, favoring the absorption, dissipation and stabilization of the load, reducing stress received by the passive osteoarticular structures, such as bone, cartilage and ligaments[34]. Additionally, the presence of controlled dynamic loads generates a cyclic stress that stimulates the elastic response of the tissue and stimulates anabolic processes such as an increase in the synthesis of proteoglycans in some tissues[14,19,24,25]. This is essential for the adequate metabolism and functioning of musculoskeletal structures such as articular cartilage[25] and the intervertebral disc[66], as well as to promote adequate bone turnover[67].

The exercise programs represent the main strategy to improve the functionality of the OMNAS, and may include qualitative strategies (improvement of engram and motor control) and quantitative strategies (improvement of muscle strength, joint flexibility and mobility, resistance, etc.), as appropriate[68]. However, it is necessary an optimal exercise load, applied to the tissue in a controlled and correctly dosed manner, which can generate a progressive adaptive process that will lead to preserving or even increasing its functional capacity and thus achieve a beneficial effect[24]. The mechanical stress generated by controlled dynamic loads, in many cases stimulates the trophic and anabolic mechanisms of the tissues[19,24,25], which favors their structural and functional adaptation, this mechanism being the foundation of therapeutic exercise programs. On the other hand, a suboptimal stimulus will not generate favorable effects and a supraoptimal load may represent a harmful stimulus.

Multimodal exercise programs should be implemented with the aim of improving the functionality of the OMNAS and favoring pain control, which can occur through indirect mechanisms such as the improvement in the ability of the neuromuscular system to absorb mechanical loads[34] or the improvement in the nutritional and metabolic processes of other tissues such as cartilage, intervertebral disc or bone[25,66,67]; However, exercise can also have direct analgesic effects such as the stimulation of analgesic mechanisms in the ascending modulation system at the level of the central nervous system, the immune system and the autonomic nervous system[68,69]. Exercise programs should include different exercise modalities according to the musculoskeletal pathology, including motor control exercises[70], joint mobility exercises[71,72], stretching exercises[73], balance and proprioception exercises[74,75], joint stabilization exercises[73,76,77], muscle strengthening exercises[71,78-80] and aerobic exercise[69,71,81]. Furthermore, the prescription must be individualized and dosed precisely and take into account the individual's comorbidities.

Therapeutic exercise should represent a cornerstone in the prevention and treatment of MPMO[82] and its effectiveness has been reported in pain of mechanical origin, as well as pain with neuropathic or nociplastic components[68,69]. Its effectiveness depends on the painful pathology to be treated and the type of exercise used[68,69,83].

In conclusion, in the context of MPMO, the factors that precede the onset of pain are mechanical overload and functional alteration of the musculoskeletal system or a combination of both. These factors may contribute to the activation of the nociceptive cascade and the onset of pain, in addition to being factors that could be related to the perpetuation and chronification of MPMO, so that the modification of loads and the improvement of the functionality of the OMNAS perhaps should be cornerstones for the prevention and treatment of MPMO.

References

1. Perrot S, Cohen M, Barke A, Korwisi B, Rief W, Treede RD; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. Pain 2019;160(1):77-82.
2. Smith E, Hoy DG, Cross M, Vos T, Naghavi M, Buchbinder R, et al. The global burden of other musculoskeletal disorders: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73:1462–1469.
3. Zhuang J, Mei H, Fang F, Ma X. What Is New in Classification, Diagnosis and Management of Chronic Musculoskeletal Pain: A Narrative Review. Front Pain Res (Lausanne) 2022;3:937004.
4. Cimmino MA, Ferrone C, Cutolo M. Epidemiology of chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2011;25(2):173-183.
5. Rollman GB, Lautenbacher S. Sex differences in musculoskeletal pain. Clin J Pain 2001;17(1):20-24.
6. Blyth FM, Briggs AM, Huckel - Schneider C, Hoy DG, March LM. The Global Burden of Musculoskeletal Pain: Where to From Here? Am J Public Health 2019;109:35–40.
7. Sifuentes-Giraldo WA, Morell-Hita JL. Diagnostic protocol of chronic musculoskeletal pain. Medicine 2017;12(27):1609-1613.
8. Ellison DL. Physiology of Pain. Crit Care Nurs Clin North Am 2017; 29: 397–406.
9. Puntillo F, Giglio M, Paladini A, Perchiazzi G, Viswanath O, Urits I, et-al. Pathophysiology of musculoskeletal pain: a narrative review. Ther Adv Musculoskelet Dis 2021;13:1759720X21995067.
10. Mertens P, Blond S, David R, Rigoard P. Anatomy, physiology and neurobiology of the nociception: a focus on low back pain (part A). Neuro-Chirurgie 2015;61:S22–S34.
11. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. Primary Care 2012;39:561–571.
12. Bonanni R, Cariati I, Tancredi V, Iundusi R, Gasbarra E, Tarantino U. Chronic Pain in Musculoskeletal Diseases: Do You Know Your Enemy?. J Clin Med 2022;11(9):2609.
13. Kirsch Micheletti J, Bláfoss R, Sundstrup E, Bay H, Pastre CM, Andersen LL. Association between lifestyle and musculoskeletal pain: cross-sectional study among 10,000 adults from the general working population. BMC Musculoskelet Disord 2019;20(1):609.
14. Radwin RG, Marras WS, Lavender SA. Biomechanical aspects of work-related musculoskeletal disorders. Theoretical Issues in Ergonomics Science 2001;2(2):153–217.
15. Kumar S. Theories of musculoskeletal injury causation. Ergonomics 2001;44(1):17-47.
16. Márquez - Gómez M. Modelos teóricos de la causalidad de los trastornos musculoesqueléticos [Spanish]. Ingeniería Industrial, Actualidad y Nuevas Tendencias. 2015; IV (14):85-102.
17. Khalsa PS. Biomechanics of musculoskeletal pain: dynamics of the neuromatrix. J Electromyogr Kinesiol. 2004;14(1):109-20.
18. Veerasammy S, Davidson JB, Fischer SL. Multi-task exposure assessment to infer musculoskeletal disorder risk: A scoping review of injury causation theories and tools available to assess exposures. Appl Ergon. 2022; 102:103766.
19. Ünal M, Akkuş O, Marcus RE. Fundamentals of Musculoskeletal Biomechanics. In: Feza Korkusuz eds. Musculoskeletal Research and Basic Science. Switzerland: Springer International Publishing; 2016: 15-36.
20. Aicale R, Tarantino D, Maffulli N. Overuse injuries in sport: a comprehensive overview. J Orthop Surg Res. 2018;13(1):309.
21. O'Neill TW, Felson DT. Mechanisms of Osteoarthritis (OA) Pain. Curr Osteoporos Rep. 2018;16(5):611-616.
22. Kodama Y, Masuda S, Ohmori T, Kanamaru A, Tanaka M, Sakaguchi T. Response to Mechanical Properties and Physiological Challenges of Fascia: Diagnosis and Rehabilitative Therapeutic Intervention for Myofascial System Disorders. Bioengineering. 2023; 10: 474.

23. Dong Y, Jiang P, Jin X, Jiang N, Huang W, Peng Y, et al. Association between long-term static postures exposure and musculoskeletal disorders among university employees: A viewpoint of inflammatory pathways. Front Public Health. 2022;10:1055374.
24. Glasgow P, Phillips N, Bleakley C. Optimal loading: key variables and mechanisms. Br J Sports Med. 2015;49(5):278-279.
25. Arokoski JP, Jurvelin JS, Väätäinen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. Scand J Med Sci Sports. 2000;10(4):186-98.
26. Irvin RE. The origin and relief of common pain. J Back Musculoskelet Rehabil. 1998; 11: 89–130.
27. Bontrup C, Taylor WR, Fliesser M, Visscher R, Green T, Wippert PM, et-al. Low back pain and its relationship with sitting behavior among sedentary office workers. Appl Ergon. 2019; 81:102894.
28. van Tulder M, Malmivaara A, Koes B. Repetitive strain injury. Lancet. 2007;369(9575):1815-1822.
29. Van Niekerk SM, Louw QA, Hillier S. The effectiveness of a chair intervention in the workplace to reduce musculoskeletal symptoms. A systematic review. BMC Musculoskelet Disord. 2012;13:145.
30. Messing K, Tissot F, Stock S. Distal lower-extremity pain and work postures in the Quebec population. Am J Public Health. 2008;98(4):705-173.
31. Nahit ES, Macfarlane GJ, Pritchard CM, Cherry NM, Silman AJ. Short term influence of mechanical factors on regional musculoskeletal pain: a study of new workers from 12 occupational groups. Occup Environ Med. 2001;58(6):374-381.
32. Kendall JC, Bird AR, Azari MF. Foot posture, leg length discrepancy and low back pain--their relationship and clinical management using foot orthoses--an overview. Foot (Edinb). 2014;24(2):75-80.
33. Nourbakhsh MR, Arab AM. Relationship between mechanical factors and incidence of low back pain. J Orthop Sports Phys Ther. 2002;32(9):447-460.
34. Zhang SN, Bates BT, Dufek JS. Contributions of lower extremity joints to energy dissipation during landings. Med Sci Sports Exerc. 2000;32(4):812-819.
35. Kell RT, Bell G, Quinney A. Musculoskeletal fitness, health outcomes and quality of life. Sports Med. 2001;31(12):863-873.
36. Pelletier R, Higgins J, Bourbonnais D. Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders? BMC Musculoskelet Disord. 2015;16:25.
37. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et-al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161:1976 –1982.
38. McGonagle D, Lories RJ, Tan AL, Benjamin. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum. 2007;56,2482-2491.
39. Mohd Isa IL, Teoh SL, Mohd Nor NH, Mokhtar SA. Discogenic Low Back Pain: Anatomy, Pathophysiology and Treatments of Intervertebral Disc Degeneration. Int J Mol Sci. 2022;24(1):208.
40. van der Kruk E, Silverman AK, Koizia L, Reilly P, Fertleman M, Bull AMJ. Age-related compensation: Neuromusculoskeletal capacity, reserve & movement objectives. J Biomech . 2021;122: 110385.
41. Tanaka R, Hirohama K, Ozawa J. Can muscle weakness and disability influence the relationship between pain catastrophizing and pain worsening in patients with knee osteoarthritis? A cross-sectional study. Braz J Phys Ther. 2019;23(3):266-272.
42. Leporace G, Batista LA, Metsavaht L, Chahla J, Oliveira T, de Oliveira LP. Correlation between muscle strength and the degrees of functionality and kinesiophobia reported by patients with chronic hip pain. BrJP. 2021;4(1):51-57.
43. Renkawitz T, Boluki D, Grifka J. The association of low back pain, neuromuscular imbalance, and trunk extension strength in athletes. Spine J. 2006;6(6):673-83.
44. Moreno Catalá M, Schroll A, Laube G, Arampatzis A. Muscle Strength and Neuromuscular Control in Low-Back Pain: Elite Athletes Versus General Population. Front Neurosci. 2018;12:436.
45. Nourbakhsh MR, Arab AM. Relationship between mechanical factors and incidence of low back pain. J Orthop Sports Phys Ther. 2002;32(9):447-460.
46. Tobias JH, Deere K, Palmer S, Clark EM, Clinch J. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence: findings of a prospective cohort study. Arthritis Rheum. 2013;65(4):1107-1115.
47. Triano JJ, Schultz AB. Correlation of objective measure of trunk motion and muscle function with low-back disability ratings. Spine (Phila Pa 1976). 1987 ;12(6):561-565.
48. P Flores-Garza PP, García-Espinoza OA, Salas-Longoria K, Salas-Fraire O. Association between ischiotibial muscle flexibility, functional capacity and pain in patients with knee osteoarthritis. Medicina Universitaria. 2017; 19(76):111-114.
49. Maciel NFB, de Oliveira Sousa C. Motor alterations in the kinetic chain in individuals with chronic shoulder pain. Gait Posture. 2022;93:183-190.
50. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. J Orthop Sports Phys Ther. 2009;39(5):364-377.
51. Sterling M, Jull G, Wright A. The effect of musculoskeletal pain on motor activity and control. J Pain. 2001;2(3):135-145.
52. Babatunde OO, Jordan JL, Van der Windt DA, Hill JC, Foster NE, Protheroe J. Effective treatment options for musculoskeletal pain in primary care: A systematic overview of current evidence. PLoS One. 2017;12(6):e0178621.
53. El-Tallawy SN, Nalamasu R, Salem GI, LeQuang JAK, Pergolizzi JV, Christo PJ. Management of Musculoskeletal Pain: An Update with Emphasis on Chronic Musculoskeletal Pain. Pain Ther. 2021;10(1):181-209.
54. Yang J, Bauer BA, Wahner-Roedler DL, Chon TY, Xiao L. The Modified WHO Analgesic Ladder: Is It Appropriate for Chronic Non-Cancer Pain? J Pain Res. 2020;13:411-417.
55. Dantas LO, Salvini TF, McAlindon TE. Knee osteoarthritis: key treatments and implications for physical therapy. Braz J Phys Ther. 2021;25(2):135-146.
56. Lee S, DE Barros FC, DE Castro CSM, DE Oliveira Sato T. Effect of an ergonomic intervention involving workstation adjustments on musculoskeletal pain in office workers-a randomized controlled clinical trial. Ind Health. 2021;59(2): 78-85.
57. Hoe VC, Urquhart DM, Kelsall HL, Zamri EN, Sim MR. Ergonomic interventions for preventing work-related musculoskeletal disorders of the upper limb and neck among office workers. Cochrane Database Syst Rev. 2018;10(10):CD008570.
58. Méndez FJ, Gómez-Conesa A. Postural hygiene program to prevent low back pain. Spine (Phila Pa 1976). 2001;26(11):1280-1286.
59. Kovacs FM, Burgos-Alonso N, Martín-Nogueras AM, Seco-Calvo J. The Efficacy and Effectiveness of Education for Preventing and Treating Non-Specific Low Back Pain in the Hispanic Cultural Setting: A Systematic Review. Int J Environ Res Public Health. 2022;19(2):825.
60. Block JA, Shakoor N. Lower limb osteoarthritis: biomechanical alterations and implications for therapy. Curr Opin Rheumatol. 2010;22(5):544-550.
61. Kinsella R, Nasser A, Menz HB, Pizzari T, Collins NJ, Semciw AI.

Effects of foot orthoses and footwear interventions on impairments and quality of life in people with hip pain: A systematic review. Musculoskeletal Care. 2023;21(4):1529-1550.
62. Pires Neves M, Sena da Conceição C, Lucareli PRG, et-al. Effects of Foot Orthoses on Pain and the Prevention of Lower Limb Injuries in Runners: Systematic Review and Meta-Analysis. J Sport Rehabil. 2022;31(8):1067-1074.
63. Zafar AQ, Zamani R, Akrami M. The effectiveness of foot orthoses in the treatment of medial knee osteoarthritis: A systematic review. Gait Posture. 2020;76:238-251.
64. Benjamin M, Hillen B. Mechanical influences on cells, tissues and organs — 'Mechanical Morphogenesis'. Eur J Morphol. 2003; 41(1):3-7.
65. Flück M. Functional, structural and molecular plasticity of mammalian skeletal muscle in response to exercise stimuli. J Exp Biol. 2006;209(Pt 12):2239-2248.
66. Belavý DL, Albracht K, Bruggemann GP, Vergroesen PP, van Dieën JH. Can Exercise Positively Influence the Intervertebral Disc?. Sports Med. 2016;46(4):473-485.
67. Chang X, Xu S, Zhang H. Regulation of bone health through physical exercise: Mechanisms and types. Front Endocrinol (Lausanne). 2022;13:1029475.
68. Chimenti RL, Frey-Law LA, Sluka KA. A Mechanism-Based Approach to Physical Therapist Management of Pain. Phys Ther. 2018;98(5):302-314.
69. Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. J Pain. 2019;20(11):1249-1266.
70. Saragiotto BT, Maher CG, Yamato TP, Costa LO, Menezes Costa LC, Ostelo RW, et-al. Motor control exercise for chronic non-specific low-back pain. Cochrane Database Syst Rev. 2016 ;2016(1):CD012004.
71. Cunningham NR, Kashikar-Zuck S. Nonpharmacological treatment of pain in rheumatic diseases and other musculoskeletal pain conditions. Curr Rheumatol Rep. 2013;15(2):306.
72. Plummer S, Leonard J. Mobilization With Movement as Therapy to Reduce Knee Pain and Increase Knee Range of Motion. J Sport Rehabil. 2022;31(7):950-953.
73. França FR, Burke TN, Caffaro RR, Ramos LA, Marques AP. Effects of muscular stretching and segmental stabilization on functional disability and pain in patients with chronic low back pain: a randomized, controlled trial. J Manipulative Physiol Ther. 2012;35(4):279-285.
74. Dal Farra F, Arippa F, Arru M, Cocco M, Porcu E, Tramontano M, et-al. Effects of exercise on balance in patients with non-specific low back pain: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2022;58(3):423-434.
75. Espí-López GV, Aguilar-Rodríguez M, Zarzoso M, Serra-Añó P, Martínez de la Fuente JM, Inglés M, et-al. Efficacy of a proprioceptive exercise program in patients with nonspecific neck pain: a randomized controlled trial. Eur J Phys Rehabil Med. 2021;57(3):397-405.
76. França FR, Burke TN, Hanada ES, Marques AP. Segmental stabilization and muscular strengthening in chronic low back pain: a comparative study. Clinics (Sao Paulo). 2010;65(10):1013-1017.
77. Smith BE, Littlewood C, May S. An update of stabilisation exercises for low back pain: a systematic review with meta-analysis. BMC Musculoskelet Disord. 2014;15:416.
78. Thorp LE, Wimmer MA, Foucher KC, Sumner DR, Shakoor N, Block JA. The biomechanical effects of focused muscle training on medial knee loads in OA of the knee: a pilot, proof of concept study. J Musculoskelet Neuronal Interact. 2010;10(2):166-173.
79. Shakoor N, Furmanov S, Nelson DE, Li Y, Block JA. Pain and its relationship with muscle strength and proprioception in knee OA: results of an 8-week home exercise pilot study. J Musculoskelet Neuronal Interact. 2008;8(1):35-42.
80. Sled EA, Khoja L, Deluzio KJ, Olney SJ, Culham EG. Effect of a home program of hip abductor exercises on knee joint loading, strength, function, and pain in people with knee osteoarthritis: a clinical trial. Phys Ther. 2010;90(6):895-904.
81. García-Correa HR, Sánchez-Montoya LJ, Daza-Arana JE, Ordoñez-Mora LT. Aerobic Physical Exercise for Pain Intensity, Aerobic Capacity, and Quality of Life in Patients With Chronic Pain: A Systematic Review and Meta-Analysis. J Phys Act Health. 2021;18(9):1126-1142.
82. Bergman S. Management of musculoskeletal pain. Best Pract Res Clin Rheumatol. 2007;21(1):153-66.
83. Hayden JA, Ellis J, Ogilvie R, Stewart SA, Bagg MK, Stanojevic S, Yamato TP, Saragiotto BT. Some types of exercise are more effective than others in people with chronic low back pain: a network meta-analysis. J Physiother. 2021;67(4):252-262.