Lateral epicondylalgia: A primary nervous system disorder

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A B S T R A C T

Lateral epicondylalgia (LE) is the most common chronic painful condition affecting the elbow in the general population. Although major advances have been accomplished in recent years in the understanding of LE, the underlying physiopathology is still a reason for debate. Differences in clinical presentation and evolution of the symptoms among patients, suggest the need for revisiting the current knowledge about subjacent mechanisms that attempt to explain pain and functional loss. Previous models have suggested that the condition is mainly a degenerative tendinopathy, associated with changes in pain pathways and the motor system. The hypothesis of this work is that LE is the clinical manifestation of a primary nervous system disorder, characterized by an abnormal increase in neuronal activity and a subsequent loss of homeostasis, which secondarily affects the musculoskeletal tissues of the elbow-forearm-hand complex. A new model for LE is presented, supported by an in-deep analysis of basic sciences, epidemiological and clinical studies.

Introduction

Lateral epicondylalgia (LE) is a challenging condition for healthcare professionals treating chronic musculoskeletal pain. Epidemiological aspects have been clearly described. LE affects 1–3% of the general population between 35 and 54 years, without preference between genders and in association with overuse activities of the elbow, forearm and wrist, such as manual work and tennis practice [1–4]. Pain can severely compromise functional performance and, in many cases, frustrate patient's expectations of recovery. It has been reported that a significant proportion of patients has symptoms for over a year, the condition can be recurrent, and 5% of the patients do not respond to conservative treatment, finally undergoing surgical intervention [5–7].

Definition and classic concepts about the etiology of LE

The understanding of the origin, perpetuation factors and effective therapeutic approach of LE are still a reason for debate. Since the original descriptions by Cyriax, changes affecting the tendon of the extensor carpi radialis brevis muscle (ECRB) (also called common extensor tendon, CET) have been considered the cornerstone of the physiopathology, clinical manifestations and treatment of LE. The most common theory claims that LE results from repetitive contraction of ECRB during manual activities [8], possibly aggravated by anatomical [9] and biomechanical [10] factors. Thus, LE is classically regarded as a degenerative overuse tendinopathy, i.e. a chronic tendon disease characterized by increased proliferation of fibroblasts, neovascularization, unstructured collagen, granulation tissue, micro-rupture and absence of inflammatory cells [11,12]. Clinically, LE is defined as pain over the lateral epicondyle during loading of wrist and fingers extensors muscles [13,14], although it has also been reported that pain is usually referred to the dorsal forearm and wrist [15]. During physical examination, pain can be reproduced by manual palpation of the CET, resisted extension of the wrist and/or the middle finger, and forced grip [14].

LE has been the target of a considerable amount of epidemiological, biomechanical and clinical studies in occupational health. One of the major issues in epidemiological research in workers with upper limb pain is the absence of a standardized classification system allowing a clear distinction between different disorders [16]. Many authors stated that the problem seems to worsen due to the fact that, in most of the cases, the symptoms and signs (e.g. diffuse pain along the arm) in a particular worker cannot be attributed to a specific condition, i.e. a recognizable injury of a certain tissue or structure that fully explains the clinical picture [16–18]. Under these circumstances, the condition is labeled as being "non-specific". Nonetheless, in this confusing scenario, a consensus exists among researchers in labeling LE as a specific tendinopathic disease [13,16,18–21]. However, defining the condition strictly as a tendinopathy due to mechanical overuse is not useful for explaining the whole clinical picture of LE. Consequently, more

comprehensive models including psychosocial factors and recent advances in pain neurophysiology have been developed in recent years.

More recent models including a role of the nervous system

Physiopathological models used in the study of chronic pain are schemes that bring together the existing epidemiological, experimental and clinical evidence, in order to determine the risk of developing certain clinical condition or the changes that a clinical entity produces at a biological level, or in other cases, aiming to link both aspects. In the field of occupational disorders of the neck and upper extremity, several models have been proposed in the last decades [18,22–27]. A common feature among all these models is that nociception was always considered as a final consequence of the structural alterations of the tissues, and the role of the peripheral and central nervous system (PNS and CNS, respectively) has been only barely defined. The involvement of the PNS in the development of work-related disorders was described in 1998 by Greening and Lynn [28], in their study on office workers with diffuse symptoms along the upper limb. Later, Lynn proposed a model in which the alterations of the chemical environment of peripheral nociceptors, inflammation of musculoskeletal tissues and mental stress separately induce pain and sensitization in patients with non-specific arm pain [19]. Although this condition may share some symptoms with LE (e.g. dorsal forearm pain), it was considered to be the result of a minor nerve lesion and to be neuropathic in nature, which is not compatible with LE. In addition, the model also attempted to distinguish non-specific arm pain from repetitive strain injuries, which according to Harrington [13] is the term used to encompass specific injuries of the upper limb due to increased activity in the workplace, such as lateral epicondylitis and carpal tunnel syndrome. Thus, no potential causal relationship between LE and the nervous system was inferred.

In 2009, an integrative model including underlying mechanisms that explain sensitization and motor changes in LE was proposed by Coombes et al. [29]. The model was based on three interrelated physiopathological components: tendon pathology, changes in the pain systems and impairments in the motor system. The authors stated that these components may have a relative contribution depending on the evolution of the symptoms, which may assist in explaining the heterogeneity in clinical presentation. However, the model appears to be restrictive in the sense that it refers only to the clinical and sensorial manifestations occurring at the lateral elbow reaching not further than the proximal forearm, and does not account for pain and sensory and nociceptive changes occurring in more distal regions [15]. Further, the same authors referred to the lateral elbow as the "original site of tissue injury", which does not match with the pain history of a great proportion of LE patients in which symptoms began distally [30]. In addition, although a potential role of neurogenic inflammation (i.e. PNS-mediated inflammation through release of neuropeptides; see Item 2) was mentioned, a more complete description of the influence of such phenomenon and its relation with tissue pathology and sensitization was not provided. Thus, albeit the model extended the horizons of clinical reasoning by moving away from the pathoanatomical approach, a shift towards a different conception of LE was not given, and the condition continued to be labeled as a tendinopathy in subsequent publications [31,32].

Criticism of previous models and author's hypotheses about LE physiopathology

Based on the available research and observations from clinical practice, the author of the current work concludes that the physiopathology of LE is still incompletely defined. Complex anatomical, biomechanical and neurophysiological interactions between musculoskeletal tissues of the elbow, forearm and hand, in conjunction with variations in initial presentation and evolution of the symptoms, strongly suggest that there is a need for revisiting the most usual

knowledge about this condition. First, unlike most frequent tendinopathies of the lower limbs (i.e. patellar and Achilles), which produce well localized pain in a specific and consistent site, the most prevalent so-called tendon disorders of the upper limb (i.e. rotator cuff pathology and LE) are characterized by referred pain. Secondly, lateral elbow pain is not frequently the initial symptom in patients pain history. Instead, pain usually begins distally, that is to say, at the hand, wrist or forearm and in other cases, in the medial aspect of the elbow, from which over the next days it propagates to the lateral epicondyle [30]. In addition, lateral elbow pain can be reproduced through mechanical provocation of other structures, such as wrist extensors muscles, radial nerve (RN) or radiohumeral joint, being also possible to significantly relieve the pain through manual manipulation of such structures [33,34]. Finally, the role of structural changes in several chronic musculoskeletal conditions is still questionable, and LE is not an exception. It has been demonstrated that the severity of the structural changes (tendon thickening, presence of hypoechoic areas, collagen fibers disruption) does not correlate with pain and function [35]. In fact, improvements in tendon structure are only occasionally used as an outcome measure after physiotherapy or medical treatment. Further, in clinical practice, imaging studies give little help both for diagnosing and determining optimal treatment and time of discharge [14]. Taken together, these observations lead to question tendinopathy as the primary feature of LE, as is usually accepted.

A possible response to these observations is that the role of the nervous system in this clinical condition is more representative and complex than previously thought. In this article, an evidence-based physiopathological model is presented suggesting that LE is the clinical manifestation of a primary disorder of the nervous system, both at peripheral and central levels, which secondarily affects musculoskeletal tissues in a regional fashion. The hypothesis is that, as a result of mechanical overuse and psychosocial factors, the regional increase in neuronal activity triggers neurogenic inflammation and neuroinflammation processes, leading to dysfunction of the homeostatic mechanisms of the nervous system associated with axonal sprouting and sustained release of neuropeptides in tissues innervated by the RN. In addition, due to the fact that ECRB is related to wrist kinematics rather than the elbow kinematics, the study of the proprioceptive and nociceptive features of this joint could be useful in order to improve the understanding of LE. The work aims to provide the scientific evidence from basic science, epidemiological and clinical research supporting the new model.

Dysfunction of homeostatic mechanisms of the nervous system. A theoretical framework for understanding clinical manifestations of le and guide clinical reasoning and management

Musculoskeletal tissues show three types of somatosensory receptors. Based on their functions, these receptors are divided into mechanoreceptors, thermoceptors and nociceptors [36]. The last ones are found in skin and deep tissues as unmyelinated free nerve endings, and reach the posterior horn of the spinal cord through type C primary afferent neurons. Under normal conditions, nociceptors are predominantly activated by non-physiologic painful stimulus that damage deep structures, such as mechanical overload, sprains, intense compression and contraction under ischemia [37]. However, it has been stated that nociceptors have a high degree of functional and chemical plasticity, which makes them capable of modifying afferent inputs before they reach the CNS, and of exerting also efferent functions on peripheral tissues (such as cell proliferation, cytokine expression, inflammation, immune responses, hormone release) through their antidromic activity [38,39]. This efferent role of afferent nociceptive fibers was suggested by Bayliss in 1901 [40]. Thanks to this unique property, the nervous system is in charge of maintaining the structure and homeostasis of musculoskeletal tissues through a complex network of regulative mechanisms that take place both at peripheral and central

levels [41]. In the PNS, nociceptors are able to initiate, potentiate and attenuate neurogenic inflammation by releasing neurochemical substances, such as substance P (SP), calcitonin gene-related peptide (CGRP) and glutamate, mainly. At spinal level, primary afferent terminals of peptidergic C fibers interact with glial and endothelial cells by releasing the same neuropeptides, increasing medullar blood flow and leading to neurogenic neuroinflammation [41]. Unlike "classic" inflammation, neurogenic inflammation and neuroinflammation are triggered and regulated by neuronal activity. These types of inflammations are not harmful by themselves, since under normal conditions of neuronal activity, they exert homeostatic functions that result in synaptic plasticity, neuroprotection, repair and regeneration. Contrarily, when nociceptors are subjected to noxious and/or repetitive mechanical stimulation, the excessive release of neurochemicals at PNS and CNS may lead to maladaptive responses or, in the worst cases, neurotoxic responses that would affect the level of reversibility of the changes and would result in chronic pathology. Both neurogenic inflammation and neuroinflammation may be self-sustained and self-amplified, and homeostatic and maladaptive reactions may occur simultaneously with anti-inflammatory reactions, making it difficult to predict the final response. For further reading about these processes, consult the review by Xanthos and Sandkühler [41].

There is increasing evidence suggesting that alterations in the homeostatic functions of the nervous system lead to axonal sprouting and sustained release of neuropeptides at peripheral and central levels. The latter is a well-recognized feature of several painful conditions [42,43], and has also been described in certain tendinopathies [44–46]. Axonal sprouting has been identified in multiple pathological states [47–50], and it represents the somatosensory and sympathetic fibers response to the release of nerve growth factor (NGF), which in turn results from mast cells degranulation [51]. In healthy musculoskeletal tissues, free nerve endings remain localized at the surrounding connective surfaces and around vessels, without being in contact with the tissue proper. But when the tissue is damaged, free nerve endings invade the tissue proper in an attempt of healing, which may result either in successful repair and adaptation, with subsequent retraction of the nervous fibers to their original location in the surrounding connective sheaths [52,53], or in failed repair, in which case nervous fibers do not retract and persist in the area of tissue injury and degeneration [52]. Increased neuropeptide release as well as axonal sprouting, may result in sensitization (i.e. an increased responsiveness of nociceptors neurons to their normal or subthreshold afferent input) and chronic pain [47,54]. Thus, these data suggest that for the development of LE there must be: 1) a stimulus increasing nociceptors activity (i.e. neuronal activity), 2) an innervated tissue, susceptible of being sensitized, and 3) a connecting nerve between target peripheral tissues and the CNS.

Stimulus increasing neuronal activity in manual workers

Neuronal activity may be abnormally increased due to repetitive mechanical loading and psychological stress [41], which are factors that may converge at the workplace and interact to initiate and exacerbate a painful condition. The relationship between work-related musculoskeletal conditions of the upper extremity and a combination of physical stressors (high exertion, repetitive movement, extreme postures and vibration) is well known [18]; on the other hand, the influence of psychosocial factors is harder to define. Transversal and longitudinal epidemiologic studies in workers have identified psychosocial and mechanical factors related to LE. It has been reported that LE is consistently associated with repetitive motion; heavy weights handling; arm, elbow and wrist sustained or extreme postures; as well as high grip forces and vibration [30,55–58]. A recent review of five longitudinal studies, which included 6922 individuals, concluded that "turn and screw" movement, wrist deviation (≥ 4 h/day), wrist torsion (≥ 2 h/day), gripping, forearm pronation ($\geq 45°$ during 40% of time), great physical exertion, and elbow flexion and extension movements are risk

factors for LE [59]. Regarding psychosocial factors, a relation between LE and both low job control and low social support from colleagues and superiors has been established [30]. The relation between physical and psychosocial factors may be causal or effect-modifying in nature: on the one side, psychosocial demands may increase muscle tension and exacerbate biomechanical stress associated with occupational tasks; on the other side, an initial physical insult may trigger a chronic dysfunction in the nervous system, both physiological and psychological, perpetuating a chronic pain state [60].

Innervation of musculoskeletal tissues by free nerve endings and potential mechanisms leading to pain and dysfunction in LE

When the above mentioned factors act in combination adding abnormal stress to the elbow-forearm-hand complex and exceeding the individual's tolerance level, it is unlikely that a single tissue or structure will absorb all the demands and develop pathological changes. Contrarily, basic science studies seem to indicate that the nervous system organizes itself and responds against overload and injury similarly in tendons, muscles and ligaments. In tendons, nerve fibers coming from the myotendinous junction enter through the endotenon, whilst fibers of plexus located at the paratenon give rise to little branches that penetrate the epitenon [61]. Nerves innervating tendons have a low number of Aα- and Aβ fibers, and a higher number of Aδ- and C fibers, responsible for nociception, and B fibers which are autonomic and exert vasomotor actions. In a healthy tendon, nerve endings do not enter the tendon proper and homeostatic regulation is modulated from the connective sheaths [61]. The role of free nerve ending in the repair of rat tendon injury has been demonstrated. The process is characterized by a phase of axonal ingrowth and release of SP and CGRP during 2–6 weeks after injury, followed by retraction to their original location between 6 and 16 weeks [62]. In humans, the presence of axonal sprouts in biopsies of patellar [63,64] and Achilles [65] tendons suggest a response to noxious mechanical stimulation and unsuccessful tendon repair. An increase in SP concentration could be associated with both pain signaling and classically described degenerative changes [52]. Although axonal sprouting has not been evidenced in ECRB tendon yet, the presence of SP and CGRP [66] and the reported increase in glutamate levels [67] strongly suggest that this could be the case in patients with LE.

Clinical and histological studies seem to indicate that the CET would not be the only structure involved in LE. The high prevalence of myofascial trigger points, which reproduce the pain at the lateral epicondyle and the dorsum of the forearm and wrist [68,69], also supports the notion that muscle tissue is at least as involved as the tendon in the physiopathology of LE [70]. The organization of PNS in muscle tissue mirrors that of the tendinous tissue: nerve endings from C and Aδ fibers outnumber those derived from Aα and Aβ, and the unmyelinated afferent fibers are predominantly located at the perimysium surrounding bundles of muscle fibers. Other locations include the arterioles, venules and sympathetic vessels adventitia, and the sheath of nerve fibers bundles. Muscle fibers themselves are not directly innervated [71]. Furthermore, a model of rats with soleus muscle inflammation showed an increased density of SP fibers expressing NGF, indicating a phenomenon of axonal growth [72]. Although more studies are needed, this evidence supports a role of PNS in muscle tissue health and repair.

As well as tendons, muscles are living tissues capable of withstanding and adapting to high levels of mechanical stress. Nevertheless, if mechanical loading of muscle fibers exceeds a threshold of intensity, either by an excessive effort of short duration or by a low-load activity of prolonged duration, damage may occur [73,74]. A model has been proposed by Visser and Van Dieën suggesting that work-related muscle disorders can be the result of muscle activity, which in turn depends on the task requirements [27]. Unfortunately, the specific threshold of muscle activity at which mechanical loading becomes harmful and provokes pain is unkonwn, and it may depend upon individual and

contextual factors acting as effect modifiers [27]. Manual work tasks usually associated with muscle disorders are often described as low intensity, static and prolonged contractions, which overload type I muscle fibers [27]. It has been demonstrated that muscle contractions around 10–20% of maximal voluntary isometric contraction, generate intramuscular pressures that exceed 20–40 mmHg and partially or completely stop blood flow [75]. Furthermore, a study in asymptomatic subjects reported that muscle activity may be increased by 45% in the wrist extensors muscles as a result of precision demands and, mainly, mental pressure during computer tasks [76], potentially aggravating the ischemia and exacerbating the activity of nociceptors. Experimental studies showed that group IV primary afferents increased their rate of discharge under conditions of ischemia after 1 min [77], which is consistent with the pain evocated in humans subjected to ischemic contractions at work. According to these data, pain originated from group IV afferents is described as dull and cramping in nature, typical of intermittent claudication, whereas pain originated from group III fibers is described as sharp and tearing [73]. In addition to the induction of ischemia, low intensity contractions lead to shear forces between active and resting muscle fibers, potentially contributing to muscle nociceptors stimulation during the release of sensitizing substances. Furthermore, the almost selective activation of type I fibers results in depletion of glycogen reserves, favoring the appearance of painful contractures [73]. Further evidence in patients with LE suggests that muscle tissue plays a key role in the clinical presentation. The only study assessing ECRB in patients with LE, investigated the pathological changes in a region located from 5 to 10 cm from lateral epicondyle [78]. Compared to controls, morphological abnormalities were significantly more frequent in patients. The findings included fiber necrosis, regeneration signs in muscle fibers and moth-eaten fibers, as well as a higher percentage of type 2A fibers. The authors suggested that the change in fiber distribution may reflect the need for an increased number of oxidative fibers in a hypoxic environment. The reported structural changes may be considered analogue to those described in chronic tendon pathology, and could be the result of a failed repair attempt made by the axonal sprouts of C fibers, although this was not hypothesized by the authors. Fig. 1 summarizes the mechanisms of muscle impairments in LE patients.

Wrist joint tissues are the final link in the chain of musculoskeletal tissues that are possibly affected by mechanical overuse. Since lateral epicondyle muscles are biomechanically related to the wrist, any potential relation between LE and articular pathomechanics should be investigated in this joint. It has been informed that LE patients grip with 11° less of wrist extension, due to diminished activity of the ECRB, which reflects an alteration of motor control [79]. Nevertheless, the articular origin of these changes and its relationship with LE were only recently proposed [80]. The ligaments of the wrist dorsum contribute to the stabilization of the joint during movements in the dart throwing motion plane, which represents the functional plane through which most of the manual tasks are performed [81,82]. By using electrical stimulation of the scapholunate interosseous ligament (SLIL), the existence of a ligamentous-muscle reflex was demonstrated [83], and ever since this structure has received great attention in the study of wrist proprioception. Ayhan et al. suggested that repetitive tasks may cause creep deformation of the SLIL, altering the reflex response and contributing to elbow pain [80]. However, the real deformation of the SLIL in regular work activities is, at least, questionable, since it has been informed that the scaphoid and the lunate show only minimal displacements in functional wrist motion [84,85], and that SLIL is substantially lengthened only at full extension [85,86]. This position strains the palmar and proximal subregions of the SLIL and may produce a ligament disruption when applied suddenly and in association to ulnar deviation [85–87], which is in most cases, the result of high-energy trauma instead of a recurrent position adopted during manual tasks. Furthermore, a histologic study showed that the dorsal subregion of the SLIL has a greater proportion of dense connective tissue with a scarce amount of mechanoreceptors, which is not consistent with the proposed proprioceptive role of the ligament [88]. On the contrary, the dorsal radiocarpal (DRC) and the dorsal intercarpal (DIC) ligaments, which are extraarticular and cross both the radiocarpal and the midcarpal joints, are richly innervated [89–91] and are subjected to a significant length increase when the wrist moves from radial extension to ulnar flexion [92]. The presence of free nerve endings associated to blood vessels in the DRC ligament suggests that this structure may be a source of neurogenic inflammation and could play a role in joint nociception [90,91,93].

Scientific evidence seems to indicate that the nervous system organization within ligaments resembles that of other musculoskeletal tissues. As was the case for tendons and muscles, basic science studies have provided evidence showing that in normal ligaments nociceptors outnumber mechanoreceptors [94,95], that they are found in the epiligament without having contact with ligamentous tissue proper [90,91,96] and that they respond to experimental injury with axonal ingrowth and subsequent retraction of new sprouts [53]. Thus, it is reasonable to assume that ligaments have the potential to react against mechanical overuse in a similar way as the aforementioned tissues. Although the role of DRC and DIC ligaments in wrist stability has been emphasized, the greater proportion of mechanoreceptors correspond to Ruffini corpuscles, while the presence of Pacini corpuscles is only occasional [82,91]. This last kind of mechanoreceptors is responsible for detecting sudden and potentially noxious joint movements, which explain why they are abundant in ankle ligaments but not in the wrist [82]. This could indicate that in terms of sensorial distribution, wrist joint may not be designed to tolerate high speed movements like those demanded in many occupational tasks, and that under such conditions the wrist may be devoid of neuromuscular protection. This notion is consistent with the results of the exposure-response analysis of Nordander et al. in male and female workers, which showed that wrist angular velocity was the most consistent risk factor for elbow-hand disorders [97]. Marras and Schoenmarklin also reported that wrist angular velocity and acceleration were the main parameters differentiating low- and high-risk jobs [98].

Dorsal wrist ligaments inflammation may have two potential consequences. First, it may act locally as a source of pressure sensitization and pain [15], which may be proximally propagated to the forearm and elbow through a sensitized peripheral nerve [99] also inducing pain at the lateral epicondyle. This is consistent with the pain history of LE patients reported during clinical consultation, and supported by a longitudinal study of manual workers, which showed that 177 out of 209 (84.6%) new cases of LE had felt pain in the forearm and in the hand within the previous three months [30]. Second, wrist overuse and inflammation might result in the loss of motor control. Associated neuromuscular impairments in patients with LE include decreased electromyographic activity of the ECRB, increased activity of the extensor digitorum communis and flexor digitorum profundus muscles and loss of wrist neutral zone during gripping, as well as grip, wrist flexion and extension and shoulder external rotation weakness [79,100,101]. Although it has been suggested that these abnormalities may be due to disuse by fear avoidance, it is possible that these changes have an arthrogenic origin and be mediated by altered afferent input from dorsal wrist capsule and ligaments.

Peripheral nerve connecting musculoskeletal tissues with the CNS

In order to complete the model, it seems necessary to identify a peripheral nerve transmitting afferent signals to the CNS as well as driving efferent responses in LE-related musculoskeletal tissues. The RN reaches the elbow anterolaterally after passing through the lateral intermuscular septum and divides into the posterior interosseous nerve (PIN) and superficial radial nerve. Branches from the RN itself and its two terminal branches are distributed all over the anterolateral aspect of the elbow and proximal forearm, to innervate the extensors and
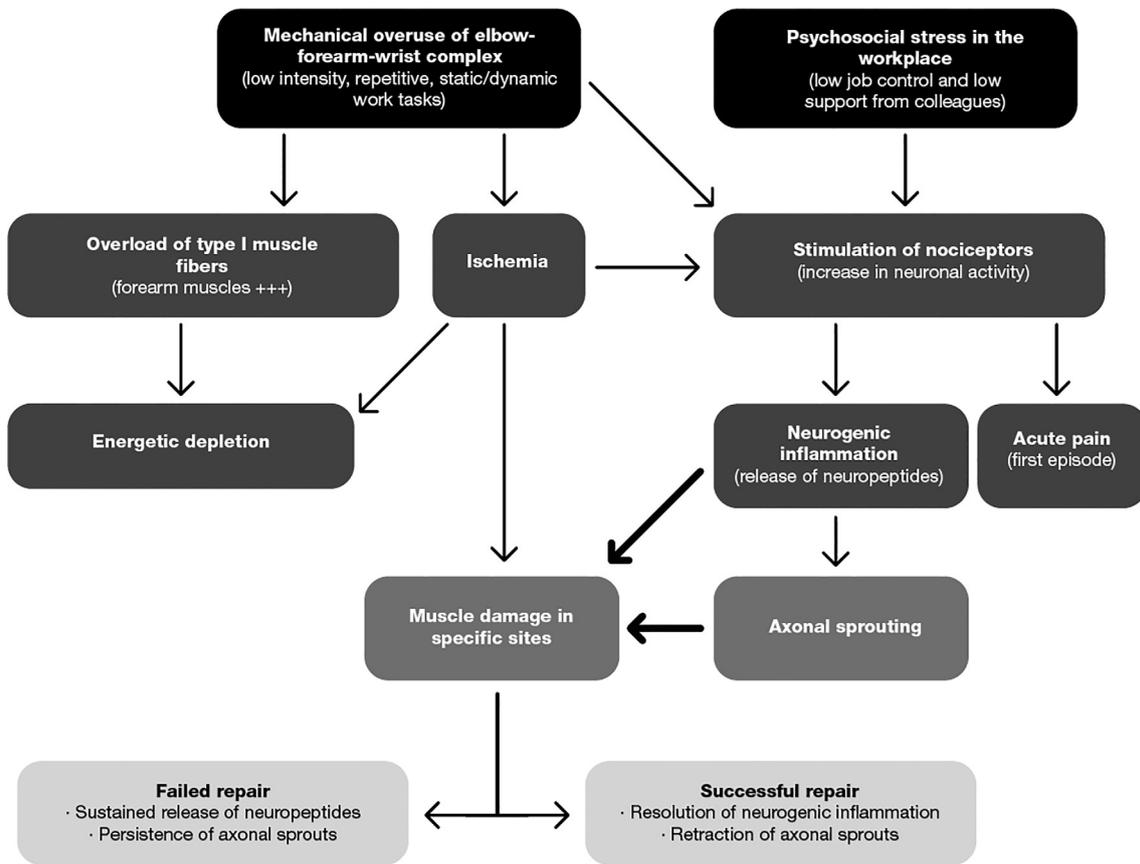
Fig. 1. Hypothesis on the physiopathology and involvement of muscle pain in LE. The combination of mechanical and psychosocial stressors results in stimulation of nociceptors, leading to neurogenic inflammation with acute or chronic pain, which in conjunction with axonal ingrowth may induce muscle damage. Overload of slow-twitch fibers and ischemia may potentiate these changes, exacerbating pain, favoring muscle fatigability and hindering muscle repair. If muscle repair fails, which may be the result of noxious mechanical loading, the sprouts of free nerve endings will remain in the site of tissue damage releasing neuropeptides, leading to progressive pain and functional loss.
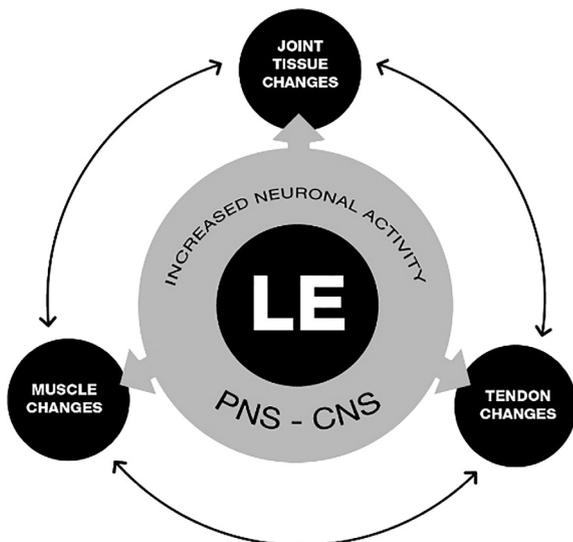
Fig. 2. New physiopathological model for LE.

supinators muscles; CET; anterolateral and posterolateral parts of the elbow capsule; radiohumeral and proximal radioulnar joints and surrounding structures such as the anular, quadrate and radial collateral ligaments [102,103]. Distally, the PIN ends as a sensory branch at the dorsal aspect of the wrist. It has been stated that sensorial receptors in dorsal wrist ligaments are derived from the PIN, which at this level is only composed of sensory fibers, and does not receive fibers from the skin or tendons [90,91,96]. Thus, a straight neuroanatomical path from the nociceptors of the musculoskeletal tissues to the CNS can be drawn. Once homeostasis is lost at the nociceptor-tissue interface in any site, the entire RN could act as a sensitized peripheral nociceptor [99], being now capable of decreasing pain threshold and inducing efferent responses in other sites of the system. This is supported by clinical studies that showed positive RN tension tested in patients with LE [104,105], and bilateral decrease in pressure pain thresholds over the RN at the lower third of the arm and the C5-C6 zygapophyseal joints [106]. Taken together, clinical data shows that pain may originate in and propagate from any of the tissues and structures related to LE through the RN, or even from the nerve itself, and that orthodromically transmitted inputs exert sensitizing actions on the spinal cord, strongly suggesting the feasibility of the proposed model.

Final remarks

A new model for LE has been presented, on the basis of the author's clinical observations as well as basic, epidemiological and clinical scientific evidence. It is proposed that the excessive increase in neuronal activity and the subsequent loss of homeostatic regulation by nociceptors that derive from the RN, as a result of mechanical and psychosocial factors, lead to axonal sprouting of the free nerve endings and sustained release of neuropeptides, both taking place peripherally, at the tissues innervated by the RN, and centrally, at the spinal cord (Fig. 2).

The presented model differs from previous ones in two ways. First, as mentioned before, it proposes that the altered homeostatic regulation

of radial nerve-innervated musculoskeletal tissues by nociceptors is the key physiopathological mechanism explaining pain and dysfunction. This notion implies that LE could be no longer acknowledged as a tendinopathy, and instead it could begin to be understood as the clinical manifestation of a primary nervous system disorder. From this physiopathological perspective, the CET would be only an additional element within a range of innervated tissues and structures that can allocate morphologic changes and act as a source of pain. Therefore, the same secondary role could be attributed to the CET, the wrist extensor muscles and the wrist joint tissues, indicating that attempting to recognize a specific structure as the initial and unique source of pain can be difficult in most cases. The second difference with previous models is that the current one includes the nociceptive features of dorsal wrist capsule and ligaments. Recently, Ayhan et al. [80] hypothesized that creep deformation of the SLIL may induce lateral elbow pain due to impairment of ligamentomuscular reflexes and, reversely, LE-associated neuromuscular impairments may alter carpal biomechanics, leading to SLIL damage. Although a model for LE was not presented by Ayhan et al., a big step towards a more comprehensive study of elbow pain in manual workers was taken. The present model additionally suggests that the DRC and DIC ligaments may be subjected to mechanical overload to a greater extent than the SLIL, and consequently they may also play a role in impairing the neuromuscular control of the wrist. Plus, the model states that joint tissues sensitization and neuroplastic changes by themselves could contribute to changes in muscle activity, without the need of a true structural damage to any ligament.

Considering the alterations in homeostatic regulation by free nerve endings through neurogenic inflammation as the key physiopathological mechanism in LE, may help to explain the heterogeneity in the sequence and progression of the symptoms from one patient to another. Epidemiological studies in workers with pain syndromes of the elbow-forearm-hand complex have provided interesting data supporting this premise. It has been reported that LE and non-specific forearm pain has almost identical biomechanical and psychosocial risk factors [30,107], and that a significant proportion of patients (48%) with diagnosis of forearm pain had also pain at the elbow [107], and vice versa, with 84.6% of LE patients having also forearm pain in the previous three months [30]. Furthermore, both conditions were highly associated with shoulder (66.5% of new cases of LE had also shoulder pain, and 67% of new cases of forearm pain had also shoulder pain) and wrist complaints. Similar results were obtained in the study by Pascarelli and Hsu, in which an exhaustive physical assessment of 485 manual workers revealed that pain was present in multiple sites and was migrating in nature [108]. The authors reported that 37% of the subjects felt pain in the hands, 29% in the wrists and 40% in the forearm and arm, and that symptoms were present concomitantly or sequentially but with a clear tendency to begin distally. Although the subjects were mainly office workers, lateral epicondylitis was diagnosed through palpation in 33% of the subjects, and the authors stated that even though tendinitis is often the primary diagnosis, it is actually one of many findings. These studies seem to indicate that LE and non-specific arm pain may share a common physiopathological pathway, and that the final expression of the dysfunction as a non-specific pain syndrome or as LE may depend on minimal differences or factors among distinct individuals. In this sense, it can be argued that LE may be more "non-specific" than what is commonly assumed. Thus, using the term *algia* -i.e. lateral epicondylalgia- rather than "lateral elbow tendinopathy" may be more appropriate, because it does not place emphasis on one structure -the tendon-whose changes are not indispensable for diagnosis, are not the only target of therapy, nor are they taken into consideration for patient discharge.

Future basic science and clinical studies will be needed to support or refute the model. The NGF-induced sprouting of free nerve endings and the presence of neuropeptides in musculoskeletal tissues related to LE would be the key findings in order to increase the likelihood of the current model. Most of the studies assessing axonal sprouting were

conducted in animals aiming at investigating the neuronal response to peripheral nerve or spinal cord injury. Only few studies using animal models of muscle exercise or damage reported the sprouting of motoneurons and formation of new endplates [109–111]. On the other hand, Reinert et al. reported the increase in SP fibers in a model of soleus muscle injury [72]. However, the author of the present work is unaware of animal studies exploring the ingrowth of free nerve endings in musculoskeletal tissues as a response to repetitive tasks of the upper limb. A wide range of tissue responses to repetitive task were reported in several animal models, including, among others, the expression of IL-1 and IL-6, SP, tumoral necrosis factor alpha and growth factors, which were associated with signs of sensitization and motor declines [112–120]. Although peripheral and central neuroinflammatory reactions were also reported [112,118], the ingrowth of free nerve endings and its role in tissue responses was not assessed. While some evidence exists of neuronal ingrowth in human tendons of the lower extremities [44,45], no evidence exists of this process in LE patients. Biopsy studies aimed at identifying the presence of NGF-sensitive free nerve endings sprouts in the ECRB tendon, forearm muscles and wrist ligaments of workers with LE could be conducted in the future.

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Conflict of interest statement

The author declares no conflict of interest related to this publication.

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