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1. Abstract

Despite advanced imaging techniques such as X-ray, MRI and ultrasound, it is often not possible to determine the exact source of nociception in musculoskeletal disorders. As many as 90% of these complaints are classified as "nonspecific," often resulting in nonspecific treatment. Diagnostic testing typically focuses on detecting tissue damage. Neuroscientist Bud Craig, however, has shown that nociception is not primarily about tissue damage, but rather about disruption of homeostasis. This insight leads to a different approach: the source of nociception is not so much a specific tissue structure, but rather the fluid in and around these structures.

Pain is primarily about cell protection, not about guarding. Shifting our focus from the hard structures to the fluids in the body creates a renewed view of musculoskeletal pathology, a better understanding of the mechanisms of action of physiotherapy, and new possibilities for treatment.

2. Introduction

The information poster for World Physical Therapy Day, Sept. 8, 2024, states, "90% of low back pain is nonspecific, meaning that no specific structure (e.g., joint, muscle, ligament or intervertebral disc) can be identified as the cause of the pain and the pain is not the result of a serious or specific underlying condition." In other words, the source of the nociception is unknown. In international guidelines, a nonspecific approach is recommended, in which education and advice to remain active are central and which also include exercise therapy and general lifestyle interventions. When symptoms become chronic, a multidisciplinary approach (such as cognitive behavioral therapy, mindfulness or graded activity) is preferred (1,2). Specific, and particularly passive, interventions are strongly discouraged. Only manual therapy has a limited role to play. The goal of treatment has shifted over the past three decades from pain reduction

to to pain management, with the aim of optimizing daily activities.

A large proportion of neck and shoulder complaints are also classified as aspecific. The underlying pathophysiology is often unclear. None of the 70 shoulder tests available is able to pinpoint the exact cause (3). Several studies show that structural changes are often found as much in people with complaints as in people without pain (4-8).

So where structural abnormalities can be found there is often no clear relationship to the pain, and where there is pain no clear source is found. How is it possible the source of nociception is still not found? But if we do a careful palpation we can distinguish very specific painful spots. These must be issues in those tissues. Are we possibly missing something? The purpose of this article is to describe a new theory that can shed new light on this confusion. If this theory is

correct examination and treatment of patients with nonspecific pain can become specific

3. Nociception

The International Association for the Study of Pain (IASP) distinguishes between three pain mechanisms: nociceptive, neuropathic and nociplastic pain. This article focuses exclusively on the first group, namely nociceptive pain. This type of pain occurs when the nervous system is

intact, but actual or imminent damage to non-neural tissue occurs, activating nociceptors. Nociceptive pain has two elements: nociception and the degree of sensitivity of the nervous system. Without nociception, there is no pain. Whether nociception leads to pain, and to what degree, depends on the sensitivity of the nervous system. The nociception is the source of pain, while the nervous system acts as a "volume knob. In this article, the focus is on nociception.

Nociceptive pain = nociception x sensitivity of the nervous system

The origin of nociceptive pain lies in the tissue, but in this area there is still much uncertainty. On the one hand, studies show that in many people without pain symptoms, imaging reveals obvious anatomical abnormalities such as osteoarthritis, degeneration and even ruptures. On the other hand, it appears that in many people with persistent pain, no tissue damage can be demonstrated. When medical examination is performed, nothing is found that explains the pain. This is known as 'nonspecific pain'.

Although it seems logical to look for a specific structure or disorder as the source of nociception, that does not get us much further. This in itself is not surprising: nociceptors do not specifically register a particular structure or condition. There are no "tendon nociceptors," "muscle nociceptors," "cartilage nociceptors," "degeneration nociceptors" or "tissue damage nociceptors." More insight may arise if we look at the stimulus that causes nociception. There are three types of nociceptors: thermosensors, mechanosensors and chemosensors.

Nociception arises from thermal, mechanical and/or chemical stimuli. The question now arises as to which of these stimuli causes nonspecific pain. Neuroscientist Bud Craig has done groundbreaking research on nociception (see box). Nociceptors turn out to be not exteroceptors, as long assumed, but enteroceptors. They continuously register

disturbances of homeostasis: thermal, mechanical and chemical. Nociceptors monitor the living environment of all our cells and are thus essential for the survival of the cell and thus the organism. According to Craig, pain is part of a homeostatic emotion, similar to hunger and thirst. Disruption of homeostasis leads to a reaction of the autonomic nervous system, a motor response and awareness. Awareness can take different forms such as tension, stiffness, discomfort and, if necessary, pain (9,10).

Craig bases his findings on research showing that all interoceptors enter at lamina I of the dorsal horn, from where they project to the autonomic centers of the brainstem and then to the thalamus and insula (9,11,13). These structures represent the center of the autonomic nervous system and the emotional brain, respectively, particularly the parts responsible for awareness (insula) and motivation (anterior cingulate cortex). Nociceptors are thus the afferent pathways of the autonomic nervous system (ANS) (14,15). Nociception leads to ANS responses that attempt to restore homeostasis, such as activating an inflammatory response, an increase in blood flow or the production of certain hormones. A motor response may also occur, such as changing sitting position after sitting still for a long time. Pain stimulates behavior that can reduce the strain on a particular part of the body so that it can recover.

The focus in pain on tissue damage can be traced back to the work of neurophysiologist C.S. Sherrington, who was the first to classify nerve cells more than a hundred years ago. The terms proprioceptors, enteroceptors, exteroceptors and nociceptors come from his research. Sherrington classified nociceptors as exteroceptors, sensors that protect the body from external dangers such as cutting, burning, bruising and tearing. In other words, they protect against tissue damage. From there the focus has been more on the integrity and quality of the "harder" tissues. With the advent of X-rays and MRI scans, the focus has shifted even further in this direction. However, neuroscientist Bud Craig has shown that nociceptors are in fact enteroceptors that monitor homeostasis. Thus, pain is not so much about tissue damage as it is about cell survival and function (9, 10, 14, 15). This is a fundamental difference. You don't need tissue damage for nociception, loss of homeostasis is enough.

Evolutionarily, this also makes more sense: it is not so relevant to the survival of the organism if a muscle tears somewhere in the body. Threat to the cell is a much greater danger. Nociception is a primal mechanism. Even unicellular organisms (with no tissue and no brain) already have a primitive nociceptive system. If you deposit a drop of acid near a unicellular organism it will move in the opposite direction, away from the danger (chemotaxis). The question to ask in pain assessment is not "where is there tissue damage?" but "where and in what way is the cell threatened?" or "where is homeostasis disturbed?"

Now back to the question: which of the three types of nociception underlies nonspecific pain? We can rule out thermonocisensors. These are activated only at temperatures where the tissue is (almost) burned or frozen, which is an uncommon situation. That mechanosensors are the primary cause seems more logical. Indeed, many patients experience (increased) pain with physical loading. However, people can lift heavy weights at work or at the gym without feeling any pain at all. All mechanosensors in the body are highly activated, but no pain occurs. The excitation threshold of these sensors is high, and pain occurs only when there is (imminent) tissue damage.

That leaves the chemosensors. But again, not every disruption of the chemical environment automatically leads to pain. For example, you can have inflammation, but as long as the tissue is not stressed, you may not experience pain. This seems to put us at an impasse. However, the key lies in the fact that when the chemical environment changes, mechanosensors become sensitized (16-22). Loading that previously caused no pain may become painful when there is an inflammation somewhere in the tissues or

when the tissue acidifies from sustained loading (see figure 1).



Figure 1:

- 1) *Despite strong activation of all mechanosensors in the body, no pain is experienced.*
- 2) *Only after a while when the tissue acidifies does the person experience pain with the same activation of mechanosensors.*

So when pain occurs with relatively light loading, it must be because the mechanosensors are sensitized. This sensitization can be caused by central sensitization (CS) and/or local sensitization. In diffuse, widespread pain, the central component is likely to be stronger,

especially when the patient reports varying locations of pain. However, when the pain is localized and reproducible on palpation, it is likely to be local sensitization, based on a chemical change in the cell's environment. Local painful spots can be identified by palpation in almost all cases of nonspecific pain. Even in fibromyalgia, often referred to as a nociplastic condition, it is not uncommon that all the pain can be provoked via pressure on trigger points (23). This cannot be explained by CS alone; something must also be disturbed locally in the tissue.

From this we can conclude that chemosensors are the primary nociceptors in musculoskeletal pain. A disturbance of the chemical environment causes the sensitization of mechanosensors, making loading painful. When there is chemical homeostasis in the tissues loading will not be painful. When we talk about the chemical environment we automatically talk about fluids, because you can only measure a chemical environment of a fluid. The only fluid to be considered is the interstitial fluid, also called the ground substance. All free nerve endings are located in this fluid, the living environment of all cells. Chemosensors continuously monitor homeostasis (15,24). A disturbance of homeostasis poses a threat to the cell and thus to the organism. Chemoreception is the primary source of the homeostatic emotion "pain," an impulse for optimal cell functioning and survival (14,15).

This means that the source of nociception is not a specific structure, such as cartilage, bone or tendon, but the interstitial fluid that surrounds these structures. This may well be the long unknown or unnamed source of nociception in nonspecific pain. In physiotherapy, we often focus on muscles, joints, nerves, menisci, and so on. However, the fluid that surrounds all these structures is an important part of the musculoskeletal system but receives remarkably little attention in physiotherapy. Fortunately, much research has been done on the ground substance in recent years.

4. The interstitial fluid or ground substance

There are different ways of looking at the body. In physiotherapy, we often approach the body primarily as a (neuro)musculoskeletal system: a skeleton of bones set in motion by the muscles attached to them. However, you can also think of the body as a flexible container filled with fluid. This container in turn contains smaller compartments, which in turn often contain even smaller compartments (25,26). All of our cells are located in these fluid-filled compartments. This all-encompassing structure, the extracellular matrix (ECM), forms the fascial system. Carla Stecco describes the fascial system as follows: "The fascial system surrounds, interweaves and permeates all organs, muscles, bones and nerve fibers. It provides the body with a functional structure and provides an environment in which all body systems can work in an integrated way" (27).

The fascial system consists, on the one hand, of the well-known collagen structures such as membranes, aponeuroses, capsules and tendons, also called the 'solid fascia'. On the other hand, there is the interstitial fluid, also called the ground substance or 'fluid fascia'. We are a multicellular organism, an alliance of cells. The core of life is the cell. Fascia protects the cells and allows them to function optimally (28). The ground substance is to cells what the sea is to fish (29). Cells get their nutrients from this fluid and excrete their wastes into it, which are then discharged through the lymphatic system (Van den Berg 2010). Constant production and discharge of the ground substance is essential for tissue cleansing and thus for a healthy cellular environment (30-32). When stagnation occurs, contamination occurs, which will lead to nociception, which can result in pain.

The main component of the ground substance is hyaluron (HA), a hydrophilic polysaccharide that can bind up to 1,000 times its own weight in water (32-34). This compound forms a gel, whose viscosity fluctuates continuously between

a more liquid and a more viscous state (35,36). Several factors influence this viscosity. For example, the gel becomes more flexible with increasing temperature, such as during a warm-up, making movement easier (37,38). About 15% of our body weight consists of ground substance, this ground substance acts as a universal "lubricant," allowing frictionless

movement (30,39-43). All of our organs, nerves, blood vessels, bones and muscles glide smoothly in this gel (44) (Figure 2). Collagen structures such as membranes, ligaments, capsules and tendons derive their suppleness and resilience from this gel.



Figure 2: Ground substance is ubiquitous in the body.

Hyaluron is an extremely important molecule because it plays a crucial role in virtually all cellular processes and pathologies (33,45-47). Its action is very complex and depends on its concentration and molecular weight, among other factors. Normally, high molecular weight HA (hmw HA) has anti-inflammatory, analgesic and pro-homeostatic properties (30,32,45,47-52). However, during acute inflammation the long HA chains fragment into low molecular weight HA (lmw HA). This is pro-inflammatory and algescic (32,47,50,51,53,54). In a normal inflammatory process, HA continues to be broken down into even smaller oligosaccharides, which quiet the inflammatory process, these are then discharged through the lymphatic system (32). Under normal conditions, new hmw HA fills the interstitial

spaces after which homeostasis is restored to the tissue. Virtually all cells in the body can produce HA (30), and within 2 to 4 days all HA is replaced (55,56). The rapid turn-over emphasizes the adaptive ability of HA in tissue regulation: homeostasis and tissue stiffness (32). Recently discovered fasciocytes, fibroblast-like cells, are specialized for HA production and are located along fascial sliding layers, such as between adjacent muscles or between muscle and bone (57). Movement stimulates both the production and removal of HA. Movement keeps everything lubricated: "motion is lotion."

The pH (acidity) of the ground substance is 7.4, i.e., slightly basic (58). Cells do not function well in an acidic environment. This is why acidity is

continuously monitored by chemosensors. Inflammation, ischemia and physical exertion cause a lowering of pH (59,60). Lowering pH is a threat to the cell and therefore a source of nociception. Gerdle (2014) describes 20 studies in which the chemical environment was measured by microdialysis in various forms of myalgia, including whiplash, nonspecific neck pain, fibromyalgia and trigger points (61). All these studies found a pro-inflammatory environment with low pH. Gibson (2009) showed that the source of nociception in delayed onset muscle soreness (DOMS) is not the muscle itself, but the fascia (or fluid container around the muscle) (62). Similar results were found by other researchers for the low back (63-65).

In most cases, disruption of homeostasis is temporary. Examples include: stiffness in the shoulders after sitting at the computer for too long, muscle soreness after intense exercise, discomfort in the buttock area from sitting on a hard bench for a long time, or morning stiffness (66). These symptoms disappear quickly with movement. Larger disturbances of homeostasis, as in trauma and periods of overuse, also often disappear without special interventions. With a properly functioning lymphatic system and adequate movement, the tissue is effectively cleansed and mobility won't be restricted.

5. Densification

The viscosity of the ground substance depends on HA concentration, molecular weight, pH and temperature (33,37,47,56). Both overload (overproduction) and underload (inadequate degradation/drainage) can lead to an increase in HA concentration and molecular mass (34,39,40,51,56). HA chains can come to overlap in this state and can form a hydrophobic macromolecular superstructure (macromolecular crowding). This results in an increase in the viscosity of the ground substance; the gel becomes more viscous and sticky. This local thickening of ground substance is called a densification (33,34,40,47,69). This decreases

lubricity, a reduced ability to glide, leading to stiffness and movement restrictions (34, 39, 40, 51, 56,70-73). Immobility (33,67), an elevated sympathetic tone (34,58), dehydration and a persistent proinflammatory environment can also contribute to the increase of viscosity of the ground substance (68).

Langevin has shown by ultrasound that the sliding between fascial layers in the low back is 20% less in people with nonspecific low back pain than in people without pain (72). It is still unclear whether these changes in fascia are the cause or consequence of low back pain (74). Kawanishi has shown that thickening of the deep and superficial fascia can reduce gliding between the vastus lateralis and superficial fascia (75). Reduced gliding leads to mechanosensors registering more tension during movement. Because they are sensitized by disruption of the chemical environment, pain can occur even with low load or at an earlier point in the movement (40,76).

The ECM acts like a sponge. Sufficient movement, stretching, compression and contortion of the tissue promotes fluid dynamics. Inactivity, on the other hand, leads to stagnation. Stagnation of lymph flow allows HA chains to entangle (32,40). A functioning lymphatic pumping mechanism and unimpeded venous drainage are necessary to remove inflammatory mediators from the extracellular compartment. Impaired vascular perfusion and/or lymphatic drainage can lead to the accumulation of inflammatory mediators in the interstitium, also called Inflammatory Interstitial Stasis. Tuckey et al. describe this as a new explanatory model for chronic pain (77).

Pro-inflammatory mediators such as TNF-alpha, IL-1b and IL-6 turn off the lymphatic pump (78). TGF-beta activates myofibroblasts, which are believed to cause pre-lymphatic or lymphatic vascular contraction and/or fibrosis. This interferes with tissue blood flow (77,79). As the viscosity of the ground substance increases, lymphatic flow slows and densifications can

compress the pre-lymphatic pathways. This creates a vicious cycle. Persistent inflammation and densifications in the tissue may eventually lead to fibrosis of the tissue (80,81). Thus, chronification of the pain can occur while no abnormalities are found on medical examination such as X-ray or MRI.

It is plausible that dehydration can enhance the formation of densifications. The maximum water binding capacity of HA is never fully achieved. Fibroblasts are connected to the collagen fibers. The tension of fibroblasts determines how much space there is in the ECM and how much water can be bound by HA (55). Sympathetic activation may affect (myo)fibroblasts, increasing tissue tension and decreasing the volume of the ECM (82). During stress, this can increase concentrations of noxious chemicals, increasing the likelihood of developing densifications (and nociception and the experience of pain). Lifestyle factors such as smoking, persistent stress, an unhealthy (read: pro-inflammatory) diet and insufficient fluid intake may possibly contribute negatively to the occurrence and persistence of densifications (28,81,83).

6. Trigger point (TrP).

A TrP can be seen as a specific form of densification. A TrP is usually described as a hyperirritable spot, a palpable nodule in the taut bands of the skeletal muscles' fascia. Direct compression or muscle contraction can elicit jump sign, local tenderness, local twitch response and referred pain which usually responds with a pain pattern distant from the spot (84).

A trigger point is formed because of contraction of sarcomeres in a number of muscle fibers at the level of the motor endplate. It is unlikely that this can be felt with as the sarcomere contraction occurs at the cellular level. Shah demonstrated with microdialysis that the chemical environment surrounding a TrP is disturbed, with the presence of several pro-inflammatory cytokines and low pH (85). This pro-inflammatory environment will

cause densification of the ground substance, which is then palpable. Not all TrPs are equally large or equally hard, which probably depends on the degree and duration of homeostasis disruption. It is also plausible that the ground substance of the endomysium or even the perimysium of the involved muscle fibers densifies, which could explain the taut band (86).

This could also explain the varying success of dry needling (DN). Sometimes it works, sometimes it doesn't, and sometimes the effect is only temporary. If the densification is still mild, DN may be sufficient, and homeostasis will be restored once the TrP is eliminated (85). However, for long-standing TrPs, treating the densification may be necessary to achieve a durable result.

Hyaluronidase is an enzyme that breaks down hyaluron. Choi's research showed that injecting hyaluronidase and lidocaine in TrPs is more effective than lidocaine alone (87). Ghasemi showed that injections of hyaluronidase are more effective than a combination of lidocaine and bicarbonate (88). This supports the hypothesis that hyaluron plays an important role in TrPs.

7. Solid fascia

7.1 Fibrosis

Densification of the ground substance limits movement between individual collagen fibers and fascial sheaths. Over time, pathological cross-links may develop between collagen fibers, leading to fibrosis. Thus, a easy reversible densification of the fluid fascia (ground substance) may eventually cause a difficult or non-reversible adhaesion of the solid fascia (80,81). Therefore, it is important to identify and treat densifications early.

Little has been written about the influence of fluid fascia denification on solid fascia function and pathology. The insights below are based partly on literature, but mainly on clinical

observations. There is still much room for further research and discussion in this area.

7.2 Reduced flexibility and permeability

All fasciae in the body are bathed in ground substance, and their suppleness depends on the fluidity of this gel. As viscosity increases, collagen fibers cannot move past each other as easily, making the fascia stiffer. When the perimysium or muscle compartments are less flexible, they are less able to adapt to the widening that occurs during muscle contraction (89). But not only this. It is plausible that also the permeability of the myofascia reduces when the gel becomes thicker. This impairs a muscle to dissipate lactate into the surrounding ground substance.

The combination of stiffer myofascia and the accumulation may lead to an increase in intrafasciomembranal fluid pressure. Hoppen describes how this increased fluid pressure can be an explanation for compartment syndromes, not only in the lower leg but in any muscle, and possibly also several other myopathies (90,91).

This could explain the pain experienced. Increased intrafascial pressure can also lead to constriction of blood vessels (92). The idea of a hardened epimysium is consistent with the observation that muscles that feel hard on palpation are not necessarily hypertonic. EMG of these muscles may show a normal signal that does not correspond to the palpated tension.

Densification of the ground substance in the epimysium could explain this observed hardness.

7.3 Resilience

Collagen structures are elastic. They can store energy when stretched and release this energy during the rebound phase (recoil). This allows for efficient movement and good shock absorption, such as in walking and running (93,94). When the ground substance becomes more viscous, this process is less efficient. More energy is lost, and forces on attachment points of muscles increase. It is readily conceivable how trochanteric or plantar heel pain could result from decreased

resilience of the iliotibial band or plantar fascia, respectively. It is possible that reduced resilience of the fascia in the lower extremities also affects higher up the chain, and contributes to complaints in the low back and neck.

7.4 Pressure on neurovascular structures

Nerves lie and move in the slippery ground substance. Densification can limit the mobility of these nerves and cause irritation. This can lead to impingement syndromes of peripheral nerves (95). This could also explain pain that occurs when nerves become "pinched" when passing through a fascial layer. Examples include meralgia paraesthetica and Anterior Cutaneous Nerve Entrapment Syndrome (A.C.N.E.S.).

8. Therapy

The ground substance is a colloid substance and is similar to paint in that way. Paint that has not been used for a time becomes more viscous, and stirring is then the solution. Short-term and minor (often global) densifications usually disappear easily by movement. People with pain symptoms due to an inactive lifestyle, for example, often need no more than coaching on becoming more active (and maybe some other lifestyle factors). However, long-term and localized densifications usually do not disappear by movement alone. In such cases, a targeted approach is required.

Densifications can be identified by history and movement function examination, and confirmed by palpation. Ultrasound, elastography and MRI can also help identify densifications/trigger points (71,73,96-100). Much work is being done to increase the reliability of these diagnostic methods (86,101,102). Menon has been able to image crowding of HA in tennis elbows with a new MRI technique (103).

Densifications are reversible and well treatable with manual techniques (32,81,103). Large HA structures can be broken down with heat and shear forces. Antonio Stecco calls this "liquify the

fascia. One way to accomplish this is by friction techniques, performed with knuckles or, less strenuously, with a metal instrument (see figure 3).

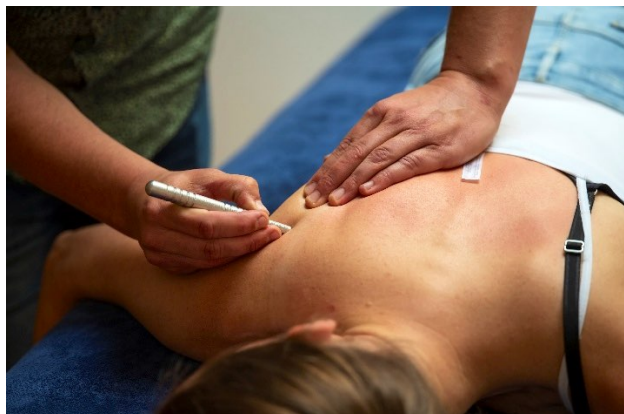


Figure 3: 'liquify the fascia' with a metal instrument

The patient usually experiences this treatment as pleasant. This treatment can be supplemented with a heat application, such as diathermy. Specific techniques, for example vibration, can further promote toxin drainage (104, 105). There is also a place here for optimizing breathing as a driving force for lymphatic drainage. It is essential that manual techniques and heat applications are not used as passive forms of treatment, as in the past. Merely heating the tissue causes the HA

superstructure to disintegrate, but it will self-aggregate again upon cooling (32). Therefore, it is important to combine these therapies with forms of exercise and training. Melt and Move! Movement can be done during manual techniques or right after. Meanwhile, there are several clinical studies supporting the effectiveness of the "liquify the fascia" approach (70,97,106-116). A number of studies show structural changes after treatment (114,116-121).

From our point of view, contrary to popular opinion, in chronic conditions there is a stronger indication for hands-on treatment. Short-lived densifications disappear with movement, but the longer the complaints exist, the harder and more extensive the densifications can be. By first reducing nociception and improving mobility, it becomes easier to start training (29, 122, 123). According to the literature, for chronic Achilles tendinopathy, you probably choose a program with gradual loading of the tendon. However, from the pathophysiology of liquids and densification, it makes sense to treat the densification in the tendon and parathenon first and then increase the load: Liquify and Load.

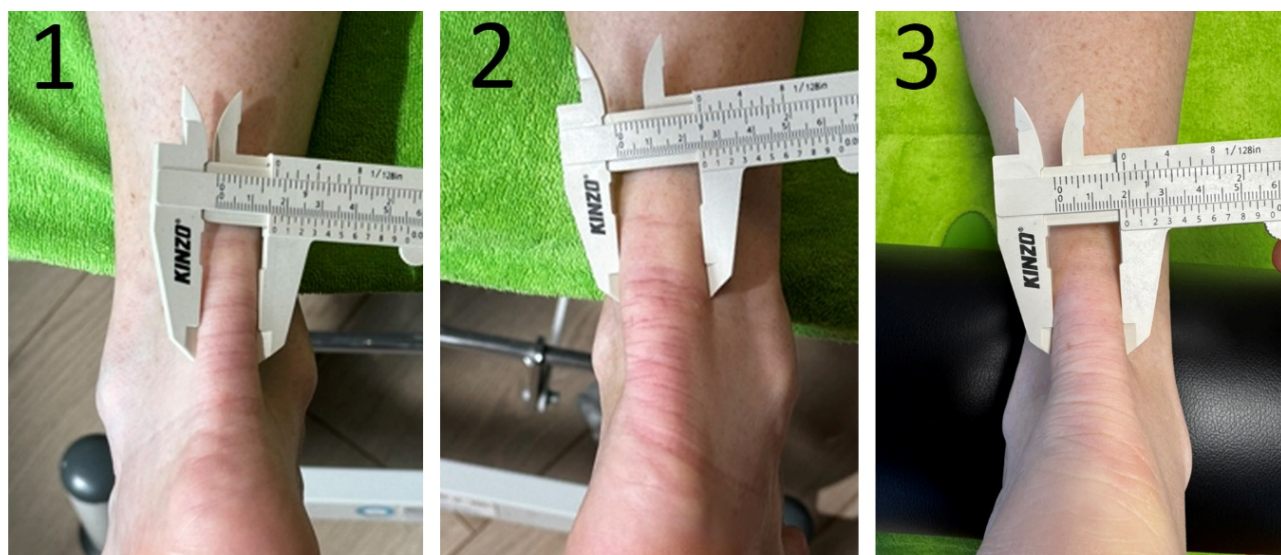


Figure 4

Woman 57 years, 20 years Achilles tendon pain, last 2 years severe. Unable to do her regular job, quit sports

- 1) Prior: Left, asymptomatic 16.5 mm
- 2) Prior: right, symptomatic 25 mm
- 3) After 4 treatments "liquify and load": right, 19 mm. Pain free, back to normal job and sports.

8.1 Pain education

Patients still often receive placebo messages, such as "you have osteoarthritis, nothing can be done" or "it's all because of your age" or "it's chronic pain, you have to learn to live with that". Or they have been told that there is no tissue damage and the pain is produced by their overly sensitive or protective brain. This often confuses patients: they cannot trust their body because they feel pain at a spot where there is 'nothing wrong'. And they cannot trust their brain because it produces pain while there is no need for it. When you make a patient feel that their pain can be generated from the soft tissues, that it's mainly about changes of fluids, this is often enlightening and reassuring. Although there is no tissue damage there is something going on in their body which is the source, not the cause, of their pain and it is (often) treatable. Once they experience that the pain can easily be reduced by liquifying the fascia (through treatment and movement) it changes the whole perspective on their symptoms.

Treatment of densifications may lead to a decrease in nociceptivity, better lubrication of all structures in the body allowing structures to glide better again, improved force distribution, improved mobility and more resilience. By recognizing and treating densifications early, potentially unnecessary examinations and surgeries can be avoided (124). Of course, attention should always be paid to causal and maintaining factors to achieve a lasting result.

9. Discussion and conclusion

In a person weighing 80 kg, about 12 kg of the body consists of ground substance, a huge amount. Besides affecting the functioning of all cells, this ground substance acts as the universal, ubiquitous "lubricant" of the body. This makes it an essential component of the musculoskeletal system. It is striking how little attention is paid to this in physiotherapy. The viscosity of the ground substance literally determines whether everything moves smoothly or not.

Bud Craig has shown that the nociceptive system has primarily a homeostatic function. Pain is essentially about the threat to the cell, not tissue damage. Nociceptors continuously monitor the balance of the fascial system. Disruption of the chemical environment of the ground substance is probably the primary cause of nociception in musculoskeletal pathology.

Researchers such as Carla and Antonio Stecco, Mary Cowman and Paolo Matteini have provided many new insights into the pathology and restoration of the ground substance. It is plausible that these insights can play a decisive role in the explanation and treatment of nonspecific complaints.

Densifications can explain the following:

- The lack of a clear relationship between pain and the findings of medical imaging.
- Symptoms like discomfort, (morning) stiffness, pain and movement restrictions.
- Decrease in mild symptoms through movement and stretching.
- Rapid reduction of symptoms through specific manual techniques, even for persistent complaints.

The knowledge of the role of ground substance in pain and movement is far from fully crystallized yet; many interesting questions remain. Some of these are:

- Which of the outcomes of physiotherapy treatment methods can be attributed to changes in ground substance?
- Specific shoulder tests don't show a strong relation between pain and structural changes. Is it possible that these tests can, however, show a relationship between a local disturbance of the chemical environment and pain?
- Where is the line between nociceptive and nociplastic pain?
- It is generally believed that stretch tolerance is increased by central pain modulation (125). Could local factors also play a role in this? Are toxins discharged during stretching,

normalizing the chemical environment and decreasing sensitization of mechanosensors?

- Is psychogenic pain exclusively psychological, or is there a nociceptive component after all? All emotions are accompanied by changes in the autonomic nervous system, and thus changes in the chemical environment of the ground substance. Can these mild changes cause pain in combination with a hypersensitive nervous system?

In summary, we believe there are sufficient reasons to replace the term 'nonspecific pain' with 'fascial pain'. In particular, looking at the role of the ground substance in pain and movement opens new avenues for further research and more specific treatments. 'Focus on fluids' could be an interesting direction of development in physiotherapy.

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