Patellofemoral Online Education

Pathophysiology of Anterior Knee Pain

Vicente Sanchis-Alfonso, MD, PhD

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INTRODUCTION

Anterior knee pain, diagnosed as Patellofemoral Pain Syndrome (PFPS), is one of the most common musculoskeletal disorders [61]. It is of high socioeconomic relevance as it occurs most frequently in young and active patients. The rate is around 15-33% in active adult population and 21-45% of adolescents [36]. However, in spite of its high incidence and abundance of clinical and basic science research, its pathogenesis is still an enigma (*"The Black Hole of Orthopaedics"*). The numerous treatment regimes that exist for PFPS highlight the lack of knowledge regarding the etiology of pain. The present review synthesizes our research on pathophysiology [53-62] of anterior knee pain in the young patient.

BACKGROUND: CHONDROMALACIA PATELLAE, PATELLOFEMORAL MALALIGMENT, TISSUE HOMEOSTASIS THEORY

Until the end of the 1960's anterior knee pain was attributed to chondromalacia patellae, a concept from the beginnings of the 20th century that, from a clinical point of view, is of no value, and ought to be abandoned, given that it has no diagnostic, therapeutic or prognostic implications. In fact, many authors have failed to find a connection between anterior knee pain and chondromalacia [52, 61]. Currently, however, there is growing evidence that a subgroup of patients with chondral lesions may have a component of their

pain related to that lesion due to the overload of the subchondral bone interface which is richly innervated.

In the 1970's anterior knee pain was related to the presence of patellofemoral malaligment (PFM) [14, 24, 26, 40]. We define patellofemoral malalignment as an abnormality of patellar tracking in the sense of lateral displacement of the patella, lateral tilt of the patella, or both, in extension, that reduces in flexion. Excessive lateral pressure syndrome (ELPS) would be a type of PFM. Although it is more common to use the term malalignment as a malposition of the patella on the femur some authors, as Robert Teitge, use the term malalignment as a malposition of the knee joint between the body and the foot with the subsequent effect on the patellofemoral mechanics [61]. For many years, PFM has been widely accepted as an explanation for the genesis of anterior knee pain in the young patient. Moreover, this theory had a great influence on orthopaedic surgeons, who developed several surgical procedures to *"correct the malalignment".* Unfortunately, when PFM was diagnosed it was treated too often by means of surgery. Currently, however, PFM concept is questioned by many, and is not universally accepted to account for the presence of anterior knee pain. In fact, the number of realignment surgeries has dropped dramatically in recent years, due to a reassessment of the paradigm of PFM.

Obviously, there are patients in whom PFM is the primary cause of their anterior knee pain but they represent in my clinical practice a small percentage of all patients with PFPS. Moreover, in my experience most of these patients were iatrogenically malaligned, that is, patients with multiple structurally/biomechanical – oriented surgeries [62]. PFM may cause pain due to cyclical soft tissue and /or bone overload.

The great problem of the PFM concept is that not all malalignments, even of significant proportions, are symptomatic. A person with PFM may never experience pain if the joint is never stressed to the point in which the tissues are irritated. Such individuals probably learn early that *"my knee hurts when I do sport"*; therefore learn to stop being active. Even more, one knee may be symptomatic and the other not, even though the underlying malalignment is entirely symmetrical (Figure 1). On the other hand, patients with normal patellofemoral alignment on computed tomography (CT) can also suffer from

anterior knee pain. Therefore, although biomechanically appealing, the malalignment theory has failed to explain the presence of anterior knee pain in many patients; so other pathophysiologic processes must exist. Moreover, PFM theory cannot adequately explain the variability of symptoms experienced by patients with PFPS (v. gr. rest pain).

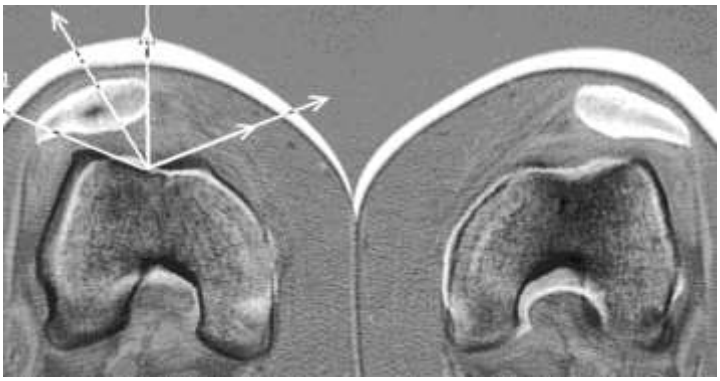

Figure 1. CT at 0º from a patient with anterior knee pain in the right knee, however the left knee is completely asymptomatic. In both knees the PFM is symmetric. (Reprinted from [61]. With kind permission of Springer Science + Business)

Finally, we must also remember that it has been demonstrated that there are significant differences between subchondral bone morphology and geometry of the articular cartilage surface of the patellofemoral joint, both in the axial and sagittal planes [71]. Therefore, a radiographical PFM may not be real and it could induce us to indicate a realignment surgery than could provoke involuntarily an iatrogenic PFM leading to a worsening of preoperative symptoms. This would be another point against the universal acceptance of the PFM theory. Moreover, this could explain also the lack of predictability of operative results of realignment surgery.

In the 1990's, Scott F. Dye, of the University of California, San Francisco, and his research group, came up with the tissue homeostasis theory [13]. According to Dye, the loss of both osseous and soft tissue of the peripatellar region homeostasis is more important in the genesis of anterior knee pain than biomechanical/structural characteristics. He suggests that patients with PFPS are often symptomatic due to supraphysiologic loading of anatomically normal knees components. In fact, patients with anterior knee pain often lack an easily identifiable structural abnormality to account for the symptoms. According to Dye theory of envelope of load acceptance, overuse or cyclical

overload of soft tissue or bone areas may explain anterior knee pain in some patients.

Patellofemoral malalignment vs tissue homeostasis theory

From a biomechanical point of view, there are two factors that can contribute to pain: (1) PFM and (2) joint loading, that depends on intensity and duration of activity. Thus, the presence of PFM would reduce the person`s envelope of loading potential; that is to say, a person with PFM and minimal to moderate joint loading can have the same overloading of the subchondral bone, which is richly innervated, as someone without PFM and high loading. Presumably, this is because PFM, reduces patellofemoral contact area which in turn would results in elevated stress across the joint [61]. Moreover, certain positions that are adopted in sports, such as maintained knee flexion and knee valgus, will contribute to increasing the overload of the subchondral bone due to the increment of the patellofemoral joint reaction and Q angle [61]. In the same sense, a maintained flexion contracture of the knee will contribute to increasing the overload of the subchondral bone due to the increment of the patellofemoral joint reaction (PFJR) [61].

In essence, the proponents of tissue homeostasis theory look at PFM as representing internal load shifting within the patellofemoral joint that may lower the threshold (i.e., decrease of the Envelope of Function) for the initiation and persistence of loss of tissue homeostasis leading to the perception of patellofemoral pain. Pain always denotes loss of tissue homeostasis. From this perspective, there is not an inherent conflict between both theories. However, these are not two co-equal theories. Tissue homeostasis theory easily incorporates and properly assesses the clinical importance of possible factors of PFM, whereas the opposite is not true.

We truly believe that both theories, are not exclusive, but complementary. In our experience, a knee with PFM can exist happily within its envelope of function, but once it is out, for example by overuse, training error, patterns of faulty sports movements or traumatism, it can be harder to get back within it, and realignment surgery could be necessary in very selected cases when non operative measures fail. The objective of surgery is to restore balance in a way

that normalizes loading of both retinacular and osseous structures without creating other aberrant or harmful effects.

OVERLOAD IN THE GENESIS OF ANTERIOR KNEE PAIN. POSTERIOR KNEE PAIN IN PATELLOFEMORAL DISORDERS. KINETIC AND KINEMATIC ANALYSIS HELP TO IMPROVE UNDERSTANDING

Powers and colleagues [48] have demonstrated by means of kinetic and kinematic analysis that female patients with PFPS presented a significant reduction in the peak vertical ground reaction force compared to the control subjects in both free walking and fast walking. They have also observed a slower gait velocity during the free and fast trials and a decrease of the stance phase knee flexion during fast walking. The reduction in knee flexion at the beginning of the stance phase could be a strategy to avoid quadriceps contraction in order to decrease the loading on the patellofemoral joint**.** Therefore, we can conclude that pain cannot be attributed to excessive lower limb loading during gait.

However, we have demonstrated that PFM could provoke, in some cases, an overload as a consequence of a modification of the gait pattern as a defense mechanism. In this sense we have found that some patients with iatrogenic medial patellar instability adopt a knee extension gait pattern to avoid an increment of the medial displacement of the patella with knee flexion, which implies an increment in the vertical ground reaction force [62]. This knee extension gait pattern obligate posterior muscles to work in a chronic manner in an eccentric condition and this situation could be responsible for posterior knee pain in some patients with patellofemoral disorders.

It is well-known that from a functional point of view ascending and descending stairs is one of the most painful activities of daily living for subjects with PFPS. Moreover, it is universally accepted that walking down stairs is more challenging that step ascent due to the level of eccentric control required during step descent.

In the healthy subject, during walking down stairs, the knee joint starts from a relatively stable extended position and flexes towards an increasingly unstable

position. The increased joint flexion causes a progressive increment in the knee flexion moment which is matched by progressively increasing eccentric muscle contraction in order to prevent collapse. In doing so, the knee extensor moment increases during walking down stairs as knee flexion occurs. As the PFJR is dependent on the magnitude of the quadriceps force and knee flexion angle, the compressive force acting between the patella and femoral trochlea during stair descent would be expected to be significant.

On the contrary, in the young patient with PFPS there is a statistically significant reduction in the knee extensor moment during walking down stairs compared to healthy control subjects. This reduction of the knee extensor moment could be a compensatory strategy used by patients with PFPS to minimize pain aggravation during activities such as walking down stairs. The reduction of the knee extensor moment, with the subsequent smaller quadriceps contraction, will provoke a decrease of the PFJR and a decrease of the loading of patellofemoral joint during pain-provoking activities such as walking down stairs. Moreover, the decrease of the active shock absorption through quadriceps muscle contraction supposes greater shock absorption through the bone and cartilage that could explain tibiofemoral pain and predispose to osteoarthritis of the knee.

One factor that could contribute to the knee extensor moment reduction could be the decrease of the stance time duration. Another strategy for reducing knee extensor moment in subjects with PFPS could be the decrease of knee flexion angles during the stance phase of stair ambulation compared to control healthy subjects. With a lesser knee flexion, the lever arm of the ground reaction force is shortened and consequently the knee extensor moment is reduced, equilibrium being achieve by fewer quadriceps contractions. This knee extension walking down stairs pattern obligate posterior muscles to work in a chronic manner in an eccentric condition and this situation could be responsible for posterior knee pain in some patients with PFPS. A decrease of the vertical ground reaction force was also observed compared to the healthy extremity. This could reflect an apprehension to load the knee joint at the beginning of the stance phase and could contribute to the knee extensor moment reduction.

PFPS patients use strategies to diminish patellofemoral joint loading during walking down stairs when compared to a pain free control group. Therefore, we can conclude that anterior knee pain cannot be attributed to excessive lower limb loading during walking down stairs.

CRITICAL ANALYSIS OF REALIGNMENT SURGERY. WHAT HAVE WE LEARNED? IN CRITICISM OF PFM CONCEPT. IS PFM CRUCIAL FOR THE GENESIS OF ANTERIOR KNEE PAIN?

As occurs with many surgical techniques, and realignment surgery is not an exception, after wide usage, surgeons may question the basic tenets and may devise clinical research to test the underlying hypothesis, in our case the PFM concept. In this way we evaluated retrospectively 40 Insall's proximal realignments (IPR) performed on 29 patients with an average follow-up after surgery of 8 years (range: 5-13 years). One of the objectives of this study was to analyze whether there was a relationship or not between the presence of PFM and the presence of anterior knee pain [61].

In our experience IPR provides a satisfactory centralization of the patella into the femoral trochlea in the short-term follow-up, that it is associated with resolution of patellofemoral pain [53]. This fact is said to support the malalignment theory. However, the success of realignment surgery may be due to factors independent of relative patellofemoral position such as dennervation of the patella, postoperative extensive rest (unload) and postoperative physical therapy. In this sense, as shown by Wojtys and colleagues [77], there are authors who have failed to show objective improvements of malalignment after isolated lateral release despite the fact that this procedure frequently lessens pain. The satisfactory centralization of the patella observed in our series is lost in the CT scans performed in the long-term follow-up in almost 57% of the cases. That is, IPR does not provide a permanent correction of patellofemoral congruence in all the cases [61]. Nonetheless, this loss of centralization does not correlate with a worsening of clinical results [61]. Furthermore, we have not found, in the long-term follow-up, a relation between the result, satisfactory versus non-satisfactory, and the presence or absence of postoperative PFM [61]. However, if according to some authors the presence of PFM is crucial for the genesis of anterior knee

pain, why we have not found differences at long-term follow-up between the result (satisfactory vs non satisfactory) and the presence or absence of PFM? We postulate that PFM could influence the homeostasis negatively, and that realignment surgery could allow the restoring of joint homeostasis when non-operative treatment of symptomatic PFM fails. Realignment surgery temporarily would unload peripatellar tissues, rather than permanently modify PFM. Once we have achieved joint homeostasis, these PFM knees can exist happily within the envelope of function without symptoms.

Moreover, in our series, 12 patients presented with unilateral symptoms [61]. In 9 of them the contralateral asymptomatic knee presented a PFM and only in 3 cases was there a satisfactory centralization of the patella into the femoral trochlea [61]. Therefore, if the presence of PFM is crucial in the genesis of anterior knee pain, how can we account for unilateral symptoms in patients with similar morphologic characteristics of their patellofemoral joints? With regards to unilateral pain in the presence of bilateral PFM, it is well known that subjects preferentially load one limb more than the other (usually the dominant limb) with high demanding activities as occurs in sports. This loading difference could be enough to cause unilateral pain. Moreover, when one knee starts to hurt, overall activity tends to decrease. Perhaps the loading on the other side is insufficient to reach the pain threshold. However, we have not found a relationship between the lateral dominance and the affected side in the cases with unilateral pain.

Finally, in 6 patients with bilateral symptoms operated on of the most symptomatic knee the contralateral knee was pain-free in the follow-up. Moreover, in my experience 91% of patients with primary PFPS improve with conservative treatment. So, if the presence of PFM is crucial in the genesis of anterior knee pain, why do symptoms disappear without any change in the patellofemoral alignment? We believe that loss of both tissue and bone homeostasis is more important than structural characteristics in the genesis of anterior knee pain.

According to Grelsamer PFM is a predisposing factor that requires a yet-unknown intermediary to trigger the pain [20]. However, we have observed that not all patellofemoral malaligned knees show symptoms, which is not surprising, as there are numerous examples of asymptomatic anatomic

variations. What is more, we have demonstrated that PFM is not a sufficient condition for the onset of symptoms. Moreover, it is not crucial for the genesis of PFPS given that there are many patients with PFPS without PFM. We can conclude that the pain generator is not the malalignment. Thus, no imaging study should give us an indication for surgery. History, physical exam, and differential injection, must point towards surgery and imaging only to allow us to confirm clinical impression.

To think of anterior knee pain as somehow being necessarily tied to PFM is an oversimplification that has positively stultified progress toward better diagnosis and treatment. The great danger in using PFM as a diagnosis is that the unsophisticated or unwary orthopaedic surgeon may think that he or she has a license or *"green light"* to correct it with misguided surgical procedures that very often make the patients' pain worse. In my experience the worst cases of anterior knee pain are those patients that have had multiple, structurally-oriented operative procedures, for symptoms that initially were only mild and intermittent.

NEUROANATOMICAL BASES FOR ANTERIOR KNEE PAIN IN THE YOUNG PATIENT: "NEURAL MODEL"

Based on our histological studies [54, 56, 57, 60], we have developed what we call *"Neural Model"* as an explanation for the genesis of anterior knee pain in the young patient.

We are fully aware that anterior knee pain can not be imputed to one single factor, but a multiplicity of factors are involved [7, 8, 17, 19, 30, 54, 56, 57, 60, 74]. The origin of pain could be in: lateral retinaculum, medial retinaculum, infrapatellar fat pad, synovium and subchondral bone. Moreover, we must also consider some influencing factors such as: overload, instability, psychological factors and gender. Moreover, it is likely that different subgroups of PFPS exist.

Our studies on anterior knee pain pathophysiology [54, 56, 57, 60] have been focused on the lateral retinaculum (67 specimens analyzed) retrieved during patellofemoral realignment surgery because there is clinical support to think

that this anatomical structure plays a key role in the genesis of anterior knee pain in the young patient [8, 17, 19, 30, 54, 56, 57, 60, 77]. According to Fulkerson [16], in patients with PFM there is an adaptative shortening of the lateral retinaculum as a consequence of the lateral displacement of the patella. With knee flexion, the patella migrates medially into the femoral trochlea [53], which produces a recurrent stretching on the shortened lateral retinaculum that may cause nerve changes such as neuromas and neural myxoid degeneration [16, 17]. Moreover, in some cases we have also performed histological studies of the medial retinaculum (13 specimens).

Patients with patellar symptoms can be divided into two groups: those with anterior knee pain and those with patellar instability. To obtain a homogeneous population we have included in our study group only those patients who had: (1) tenderness over the lateral retinaculum and excessive lateral tightness in the cases in which the main symptom was pain, and instability in the lateral direction in the cases in which the main symptom was instability, (2) PFM demonstrated with CT, (3) no previous knee surgery, (4) no peripatellar tendinosis and bursitis, and (5) no associated intraarticular pathology (synovitis, meniscal tears, ACL/PCL tears, osteoarthritis) confirmed arthroscopically. Given that our objective was to study “pain” patellar instability group was used as control group.

Morphologic neural changes into the lateral retinaculum

Some studies have implicated neural damage into the lateral retinaculum as a possible source of pain in the young patient. In 1985, Fulkerson and colleagues [17] described for the first time nerve damage (demyelination and fibrosis) in the lateral retinaculum of patients with intractable patellofemoral pain requiring lateral retinacular release or realignment of the patellofemoral joint. The changes observed by these authors in the retinacular nerves resembled the histopathologic picture of Morton's interdigital neuroma. Later, in 1991, Mori and colleagues [43] found degenerative neuropathy into the lateral retinaculum in patients with anterior knee pain. Like theses authors, we [54, 60] have also observed in many cases, into the lateral retinaculum, chronic degenerative non-specific changes in nerve fibers, with myxoid degeneration of the endoneurium, retraction of the axonal component and

perineural fibrosis (Figure 2A). Likewise, a smaller group of specimens presented nerve fibers mimicking amputation neuromas seen in other parts of the body [54, 60] (Figure 2B). Regarding neuromas, we have seen a clear relationship between their presence and anterior knee pain. In contrast, we have found no relationship between neural myxoid degeneration and pain.

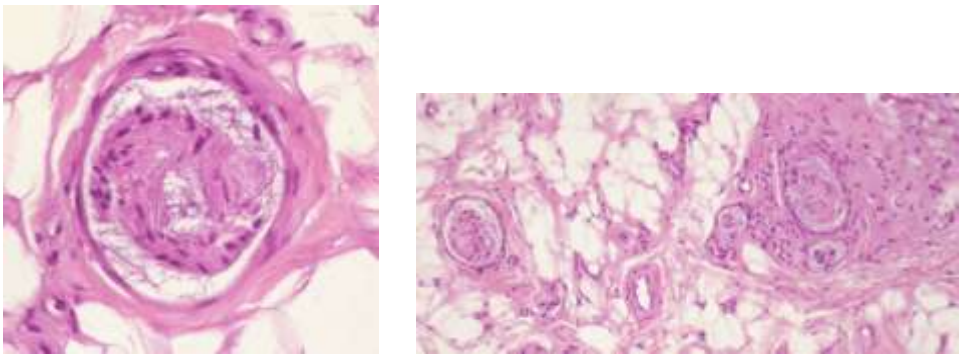

Figure 2. Histologic features of a nerve with neural myxoid degeneration (A), and a tissular neuroma (B) in the lateral retinaculum. (Hematoxylin-Eosin stain). (Reprinted from [54]. With permission of SAGE Publications).

Nerve damage occurs diffusely in the affected retinaculum, and therefore one must consider the possibility of multiple neurologic sequelae in the peripatellar region. A possible consequence of this nerve damage could be an altered proprioceptive innervation [17]. Baker and colleagues [28] observed abnormal knee joint position sense (proprioception) in subjects with PFPS. This is in agreement with the clinical study of Jerosch and Prymka in 1996 [29], that revealed a highly significant reduction in knee proprioception after patella dislocation, explained by the damage of neuroproprioceptive fibers [29, 75].

Current research shows the importance of proprioceptive information from joint mechanoreceptors for proper knee function. Connective tissues, in addition to their mechanical function, play an important role in transmitting specific somatosensory afferent signals to the spinal and cerebral regulatory systems. Thus, the giving-way in patients with PFPS can be explained, at least in part, because of the alteration or loss of joint afferent information concerning proprioception due to the nerve damage of ascendent proprioception pathway or decrease of healthy nerve fibers capable of transmitting proprioceptory stimuli [54]. In conclusion, it seems likely that, to a certain degree, the instability in patients with PFPS depends not only on

mechanical factors (such as patella alta, soft tissue dysplasia, and patellar and trochlear dysplasia) but also on neural factors (proprioceptive deficit both in the sense of position, and in slowing or diminution of stabilizing and protective reflexes) [20, 29, 75]. Jensen and colleagues [28] demonstrated an abnormal sensory function in the painful and non-painful knee in some subjects with long lasting unilateral PFPS. A dysfunction of the peripheral and/or the central nervous system may cause neuropathic pain in some individuals with PFPS.

Hyperinnervation into the lateral retinaculum and anterior knee pain. Immunohistochemical analysis for neural markers

Our studies have implicated hyperinnervation into the lateral retinaculum as a possible source of anterior knee pain in the young patient [54, 60]. Thus, we found an increase in the number of nerves in the lateral retinaculum of patients with painful PFM, there being higher values in those with severe pain compared with those with moderate or light pain [60]. Moreover, we have seen that the lateral retinaculum of the patients with pain as the predominant symptom showed a higher innervation pattern than the medial retinaculum or the lateral retinaculum of patients with patellar instability [56]. This nerve ingrowth, consisted of myelinated and unmyelinated nerve fibers (Figure 3) with a predominant nociceptive component [56].

The nociceptive properties of at least some of these nerves are evidenced by their substance P (SP) immunoreactivity. SP, which is found in primary sensory neurons and C fibers (slow-chronic pain pathway), is involved in the neurotransmission pathways of nociceptive signals [2, 4-6, 11, 15, 22, 32-34, 47, 76, 77]. SP was detected in the axons of big nerve fibers, in free nerve endings, and in the vessel walls in some patients with pain as predominant symptom [56] (Figure 4). Nociceptive fibers, that is, neural fibers with intra-axonal SP, were in a lower number than NF fibers, indicating that not all the tiny perivascular or interstitial nerves were nociceptive [56]. Interestingly, our finding that SP-fibers were more abundant in the lateral retinaculum than in its medial counterpart reinforce the role of the lateral retinaculum as a main source of pain in these patients [56]. Moreover, we have observed that the number of these nociceptive fibers was higher in PFM patients suffering from

pain as main symptom than in those with instability as predominant symptom (with little or no pain between instability episodes) [56].

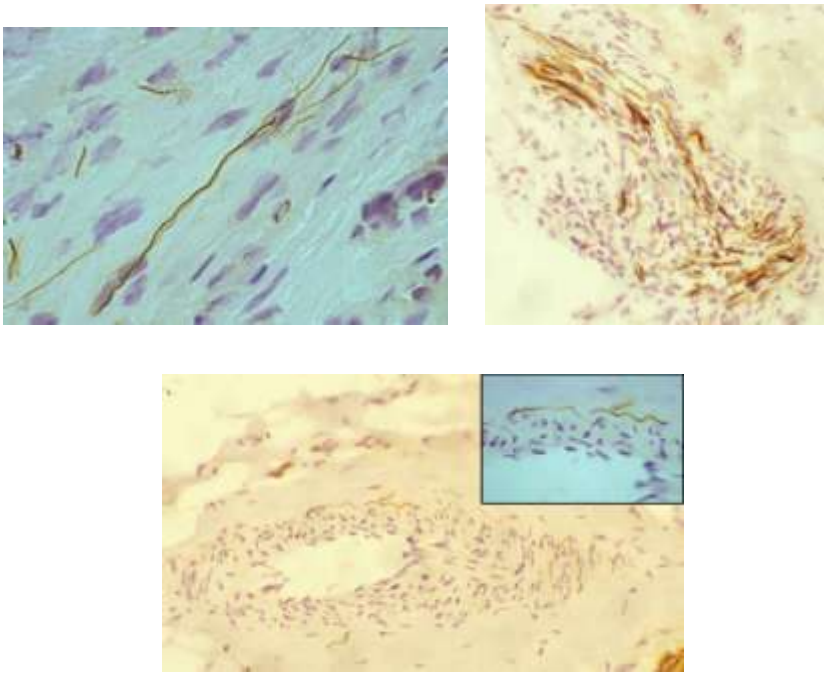

Figure 3. Free nerve endings (A). Neuroma showing the richness in free nerve endings (B). Vascular innervation (C) (Neurofilaments, hematoxylin counterstained). (Reprinted from [56]. With permission of SAGE Publications).

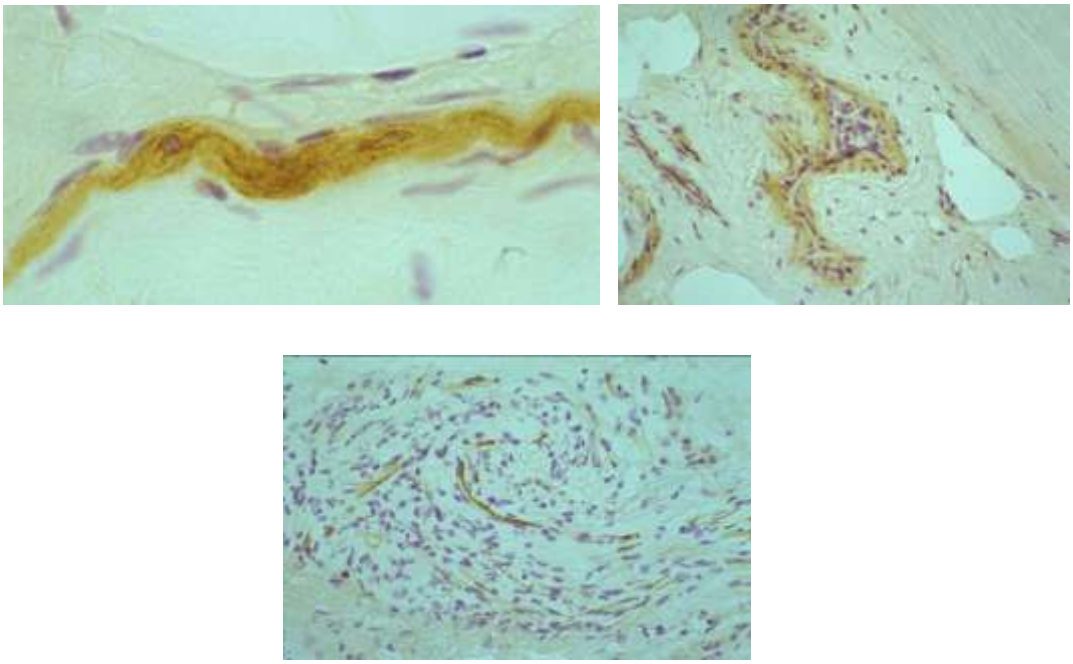

Figure 4. Substance P is present in the axons of the nerves and in the free nerve endings with a granular pattern (A), and can be observed in the vessel walls in some patients with a painful clinic (B). Neuromas are rich in nociceptive axons, as can be demonstrated studying substance P (C). (Immunohistochemistry for Substance P. Frozen sections) (Reprinted from [56]. With permission of SAGE Publications).

Nerve ingrowth is mostly located within and around vessels [56, 60] (Figure 5). Thus, we have seen, into the lateral retinaculum of patients with painful PFM, S-100 positive fibers in the adventitial and within the muscular layer of medium and small arteries, resembling a necklace. S-100 protein is a good marker when studying nerves, because of its ability to identify Schwann cells that accompany the axons in their myelinated part. It is well known that myelinated fibers lose their myelin sheath before entering into the muscular arterial wall, but this was not the case in our patients. Since we were studying by S-100 immunostaining only the myelinated fibers, and the myelin sheath is supposed to be lost before the nerve enters the muscular arterial wall, we were surprised by the identification of S-100-positive fibers within the muscular layer of medium and small arteries. Therefore, our findings may be considered as an increase in vascular innervation. We have demonstrated that vascular innervation was more prominent (94%) in patients with severe pain, whereas we found this type of hyperinnervation in only 30% of the patients with light or moderate pain [60]. Our findings are in agreement with the statement of Byers that postulated in 1968, that pain in the osteoid osteoma could be generated and transmitted by vascular pressure-sensitive autonomic nerves [9].

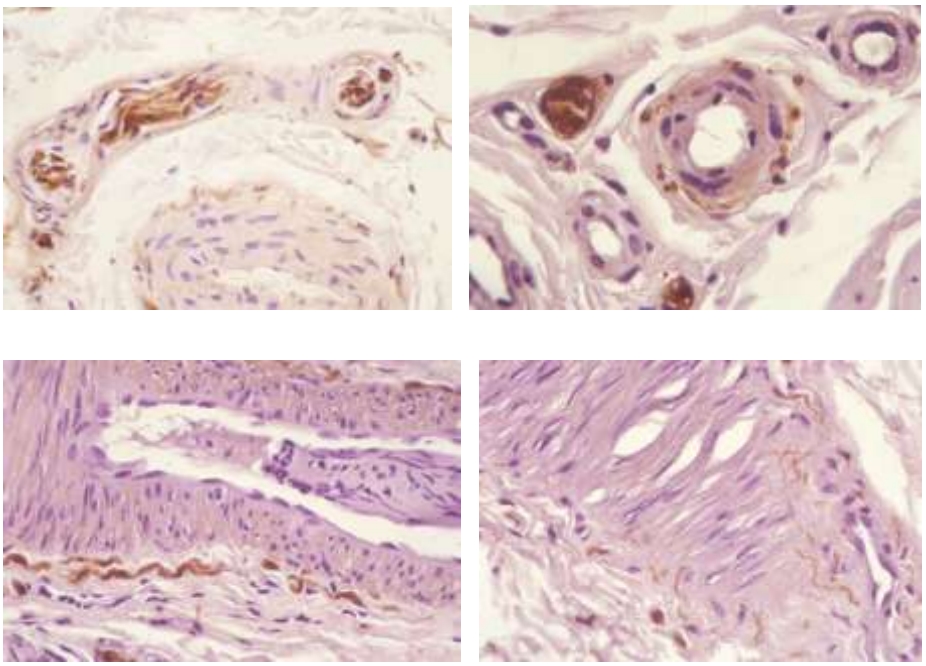

Figure 5. An increase in periadventitial innervation is detectable in our patients expressed as a rich vascular network made up of tiny myelinated fibers that, from the arterial adventitia, enter into the outer muscular layer, conforming a necklace. (Immunohistochemistry for protein S-100) (Reprinted from [54]. With permission of SAGE Publications).

In reviewing the literature, we have seen that hyperinnervation is also a factor implicated in the pathophysiology of pain in other orthopaedic abnormalities such as chronic back pain, and jumper's knee [11, 15]. On the other hand, pain has also been related with vascular innervation in some pathologies as is the case in osteoid osteoma [23], where the authors found an increase in perivascular innervation in all their cases, postulating that pain was more related with this innervation than with the release of prostaglandin E_2. Grönblad and colleagues [21] have also found similar findings in the lumbar pain of the facet syndrome. Finally, Alfredson and colleagues [3] related pain in Achilles tendinosis with vasculo-neural ingrowth.

We have demonstrated that hyperinnervation is associated with the release of neural growth factor (NGF), a polypeptide that stimulates axonogenesis [57]. NGF adopted a granular pattern in the cytoplasm of Schwann cells of the thick nerve fibers and in the muscular wall of the arterial vessels and the amount of staining for this neurotrophin was related with increased perivascular innervation [56]. NGF has two biologically active precursors: a long form of approximately 34 kD of molecular weight, and a short form of 27 kD [12]. We have found, in the lateral retinaculum of patients with painful PFM, the 34 kD precursor. The fact that some of the nerve fibers of the lateral retinaculum express NGF means that these nerve fibers must still be in a proliferative phase [57]. As expected, we found that NGF is higher in patients with pain that in those with instability as the main symptom [57]. Gigante and colleagues [19] have also found NGF and TrkA (the NGF receptor) expression into the lateral retinaculum of patients with PFM, but not in patients with jumper's knee or meniscal tears.

However, NGF is related not only to neural proliferation in vessels and perivascular tissue but also to the release of neuroceptive transmitters, such as substance P [38]. We postulate that both mechanisms are involved in the pathogenesis of anterior knee pain in patients with PFM. Thus, we suggest that two pathobiological mechanisms may lead to symptomatic PFM: (1) pain as the main symptom, with detectable levels of NGF that cause hyperinnervation and stimulus of SP release, and (2) instability as the predominant symptom, with lower levels of local NGF release, less neural proliferation and less nociceptive stimulus [57]. This means that there must be other factors acting on a PFM to conduct it versus pain or instability as the

main symptom. Maybe, PFM may not have anything to do with the appearance of pain (PFM = "non participating guest"). In other words, symptoms appear to be related to multiple factors with variable clinical expression, and our imperfect understanding of these factors may explain the all-too-frequent failure to achieve adequate symptom relief with the use of realignment procedures.

The question is: which are the mechanisms that stimulate NGF release in these patients? We hypothesize that periodic short episodes of ischemia could be the primary mechanism of NGF release, hyperinnervation, and therefore could be implicated in pain, at least in a subgroup of patients with PFPS.

WHICH IS THE BASIC CAUSE OF THE DISEASE? ROLE OF ISCHEMIA IN THE GENESIS OF ANTERIOR KNEE PAIN. "LOSS OF VASCULAR HOMEOSTASIS"

Despite the numerous publications concerning PFPS, the basic cause of the disease, that is the pain-provoking mechanism, is controversial. Rethinking the pathogenesis of PFPS and exploring new pain mechanisms could lead to changes in the assessment and management of this syndrome. The findings in our studies are in agreement with the biologically orientated perspective of the genesis of pain proposed by Scott Dye. Our results indicate that vascular problems also affect the tissue homeostasis. We propose the loss of vascular homeostasis as an intrinsic mechanism of pain in a subgroup of anterior knee pain patients.

Definition of tissue homeostasis, ischemia and hypoxia

The term homeostasis is defined to mean the maintenance of constant conditions in the internal environment. The concept of tissue homeostasis involves all the molecular and biochemical processes that result in the normal maintenance of living structures and which restores in an automatic biologic process homeostasis (healing) following a perturbing event or series of events (overuse). At present, osseous homeostasis can be sensitively and geographically manifested by the use of PET scans (Positron Emission Tomography) with the use of flourine[18]. However, no method exists to sensitively and geographically manifest soft tissue homeostasis. Clinically, the

presence of musculoskeletal soft tissue homeostasis is manifested by the absence of pain, tenderness, warmth, or swelling, while the loss of musculoskeletal soft tissue homeostasis is most often indicated by the presence of pain, tenderness, warmth, and swelling, etc., the classical signs of inflammation.

Hypoxia is a pathological condition in which the body as a whole (generalized hypoxia) or in part (tissue hypoxia) is deprived of an adequate supply of oxygen. It could be the result of a reduced supply of arterial blood or venous stasis (ischemic hypoxia), insufficient oxygen saturation (hypoxic hypoxia), or low hemoglobin (anemic hypoxia). Ischemia is an absolute or relative shortage of blood supply caused by vasoconstriction or blockage of the blood vessels supplying or draining the tissue.

Basic science

According to some authors NGF synthesis can be induced by ischemia [1, 35, 78]. Moreover, it has been shown that NGF stimulates neural sprouting and hastens neural proliferation in vessels walls [25, 31], and it is just the pattern of hyperinnervation that is seen in the lateral retinaculum of patients with painful PFM [54, 56, 60]. Similar changes have been studied in animal models and are present in the coronary innervation of patients with myocardial infarcts and brain ischemia [1, 31, 35]. Thus, we hypothesize that short episodes of tissular ischemia, due to a mechanism of vascular torsion or vascular bending, may be the main problem in painful PFM [56, 57, 60]. Vascular bending could be induced mechanically by medial traction over the retracted lateral retinaculum, due to PFM, with knee flexion.

We have demonstrated histologic retinacular changes associated with hypoxia in painful PFM [60]. In this way, we find lesions that can lead to tissular anoxia such as arterial vessels with obliterated lumina and thick muscular walls [60] and, in addition, we find other lesions that are a consequence of ischemia such as infarcted foci of the connective tissue, myxoid stromal degeneration and ultrastructural findings related with anoxia (degenerated fibroblasts with autophagic intracytoplasmic vacuoles, endothelial cells with reduplication of the basal lamina, young vessels with endothelial cells

containing active nuclei and conspicuous nucleoli and neural sprouting) [51, 60, 68]. We ought to bear in mind that, at experimental level, it has been found that neural sprouting finishes when NGF infusion ends [25].

Another phenomenon related with ischemia is angiogenesis, given that chronic ischemia leads to VEGF-release, inducing hypervascularization in order to satisfy the needs of the tissue [67]. We have performed a quantitative analysis of vascularization into the lateral retinaculum excised at the time of surgical patellofemoral realignments using a pan-vascular marker, anti-Factor VIII-related antigen [60]. Thus, we found an increase in the number of vessels in the lateral retinaculum of patients with painful PFM, there being higher values in the severe pain group compared with those of moderate or light pain [60]. Moreover, as expected, we found a positive linear correlation between number of vessels and number of nerves [60].

Tissular ischemia induces vascular endothelial growth factor (VEGF) release by fibroblasts, synovial cells, mast cells or even endothelial cells [37, 41, 44, 80]. Following these principles, we performed a study of VEGF expression into the lateral retinaculum of patients with PFM by immunohistochemistry and immunoblot [60]. VEGF is a potent hypoxia-inducible angiogenic factor that causes hypervascularization [27, 37, 39, 41, 50, 67, 72]. VEGF release begins 8 hours after hypoxia and the peptide disappears in 24 hours, if the ischemic crisis is over [60, 61]. Therefore, VEGF positivity reflects that, at this moment, we face an ischemic process, or better said, we are between 8 and 24 hours from the onset of the transitory ischemic episode. However, given the fact that the average life of VEGF is very short, its negativity has no significance regarding the presence or not of a transitory ischemic process.

Although this process has been well documented in joints affected by rheumatoid arthritis and osteoarthritis [27, 44, 49, 80] it has never been documented in PFM until our study [60]. In our series, VEGF production was seen in stromal fibroblasts, vessel walls, certain endothelial cells and even nerve fibers, as much in axons as in perineurum [60] (Figure 6). We complemented immunohistochemistry to identify and locate VEGF with immunoblotting so as to detect even minimal expression of VEGF. Our immunohistochemical findings were confirmed by immunoblot analysis.

VEGF levels were higher in patients with severe pain than in those with light-moderate pain whereas the protein was barely detectable in two cases with light pain [60] (Figure 7).

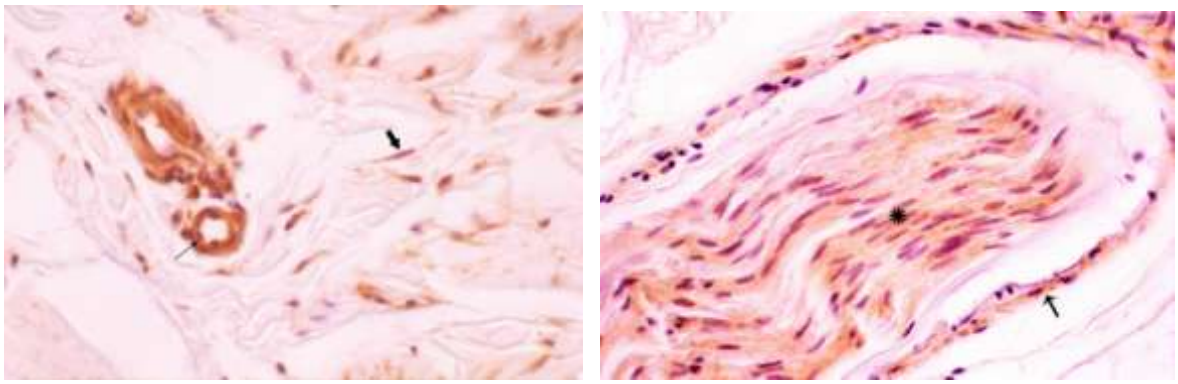

Figure 6. (a) VEGF is present in small vessels (wall and endothelium) (thin arrow) and in perivascular fibroblasts (thick arrow) in patients with moderate-severe pain. (b) Some cases have VEGF expression even in the perineural shift (thin arrow) and inside the axons (asterisk). (Immunohistochemistry for VEGF). (Reprinted from [61]. With kind permission of Springer Science + Business)

Figure 7. Immunoblotting detection of VEGF, showing a thicker band in cases with severe pain, whereas it is hardly expressed in two patients in whom instability and not pain was the main problem. (Severe pain: cases 2,3,10; moderate pain: cases 1,5,8 and light pain: cases 4,6,7,9). (Reprinted from [61]. With kind permission of Springer Science + Business)

VEGF expression is absent in normal joints [27] although inflammatory processes can stimulate its release [27, 49]. In such cases, synovial hypoxia secondary to articular inflammation is supposed to trigger VEGF production [27]. However, we have not observed inflammatory changes into the lateral retinacum in our cases [54, 60]. Furthermore, it has been reported that peripheral nervous system hypoxia can simultaneously trigger VEGF and NGF synthesis via neurons [10] inflammatory or stromal cells [1, 35, 78].

VEGF induces hypervascularization and NGF induces hyperinnervation. Both facts have been observed in our cases [54, 60]. We have concluded that ischemia could be the main trigger for the pain in PFPS, at least in a subgroup of patients with PFPS.

Clinical studies

We believe that PFPS may be attributable to vascular disturbance. However, the role of vascular insufficiency in PFPS has not been studied extensively from a clinical point of view. In fact, up to now only few clinical papers allude to the possibility of hypoxia as a factor in the pathogenesis of anterior knee pain.

Sandow and Goodfellow [63] investigated the natural history of anterior knee pain in adolescents. They observed in a study sample of 54 adolescent girls that 9 out of 54 (16.7%) had pain that was aggravated by cold weather. According to Selfe and colleagues [64], the proximal part of the rete patellae is very superficial, and therefore it is vulnerable to thermal environmental stress, resulting in greater hypoxia during cold weather. More recently, Selfe and colleagues [65] studied the clinical outcome in a sample of patients categorized as hypoxic, that is to say PFPS patients with *"cold knees"* (his/her legs felt cold even in warm surroundings). Fourteen out of 77 (18%) of the patients were classed as *"cold sufferers"* (a percentage very similar to that of Sandow and Goodfellow). They studied local hypothermia by means of infrared thermography. The authors concluded that the patients categorized as hypoxic reported greater pain levels and responded worse to an exercise based treatment than non-hypoxic patients. Gelfer and colleagues [18], using single-photon emission computed tomography (SPECT), also found a relationship between transient patellar ischemia following total knee replacement and clinical symptoms of anterior knee pain. In the same sense Naslund [45] also observed, using photoplethysmography, which is a reliable technique for estimating blood flow in bone tissue, that an ischemic mechanism (decreased blood flow in the patellar bone) is involved in the pathogenesis of pain in PFPS. Moreover, Naslund [45] also observed in half of PFPS patients an accelerated bone remodelling in any of the bony compartments of the knee joint that may be due to a dysfunctioning sympathetic nervous system and cause intermitent ischemia and pain. Selfe and colleagues [64] classified

anterior knee pain syndrome patients into three groups: hypoxic, inflammatory, and mechanical. However, ischemia may be the pain-provoking factor in all three groups given that inflammatory changes can develop not only after ischemia but also after mechanical damage to the vascular system [45, 79]. Ischemia could be caused by higher intraosseous pressure, redundant axial loading or decreased arterial blood flow [45].

AUTHOR'S PROPOSED ANTERIOR KNEE PAIN PATHOPHYSIOLOGY (see figure 8)

We hypothesize that short and repetitive episodes of tissular ischemia, due maybe to a mechanism of vascular torsion or vascular bending, which could be induced by a medial traction over a retracted lateral retinaculum, could trigger release of NGF and VEGF on PFM. Once NGF is present in the tissues, it induces hyperinnervation, attraction of mastocytes, and substance P release by free nerve endings [38]. In addition, VEGF induces hypervascularization and plays also a role increasing neural proliferation.

Free nerve endings, slowly adapting receptors that mediate nociception, are activated in response to deformation of tissues resulting from abnormal tensile and compressive forces generated during flexoextension of the knee, or in response to the stimulus of chemical agents such as histamine, bradykinin, prostaglandins, and leukotrienes [32, 69, 70]. Therefore, SP is released from peripheral endings of nociceptive afferents as a result of noxious chemical or mechanical stimulation. The nociceptive information relayed by these free nerve endings is responsible, at least in part, for the pain.

Once SP is liberated on the connective tissue, the neuropeptide induces as well the release of prostaglandin E2, one of the biochemical agents known to stimulate nociceptors [2]. The activation of nociceptive pathways by prostaglandins could be one of the many mechanisms involved in the transmission of pain from knees with PFM. Moreover, SP stimulates mast cells, facilitating a degranulation process, which can liberate in the media another nonneurogenic pain mediator, the histamine [22]. Numerous mast cells have been identified into the lateral retinaculum of our patients [61]. Mast cells have been also related with the release of NGF [46, 56],

contributing to the hyperinnervation and indirectly provoking more pain. Furthermore, SP has been shown to induce the release of collagenase, interleukin-1 and tumor necrosis factor-alpha (TNF) from synoviocytes, fibroblasts and macrophages, that could participate in the genesis of patellar instability by degradation of soft tissues [2, 5]. SP has recently been implicated as well in bone resorption both in vitro and in vivo, which can explain at least in part the osteoporosis associated in many cases of anterior knee pain [66]. Finally, SP and VEGF stimulate endothelial cell proliferation and migration [6], which are essential in the development of a new vascular network that may promote tissue repair, but indirectly maintain the vicious circle.

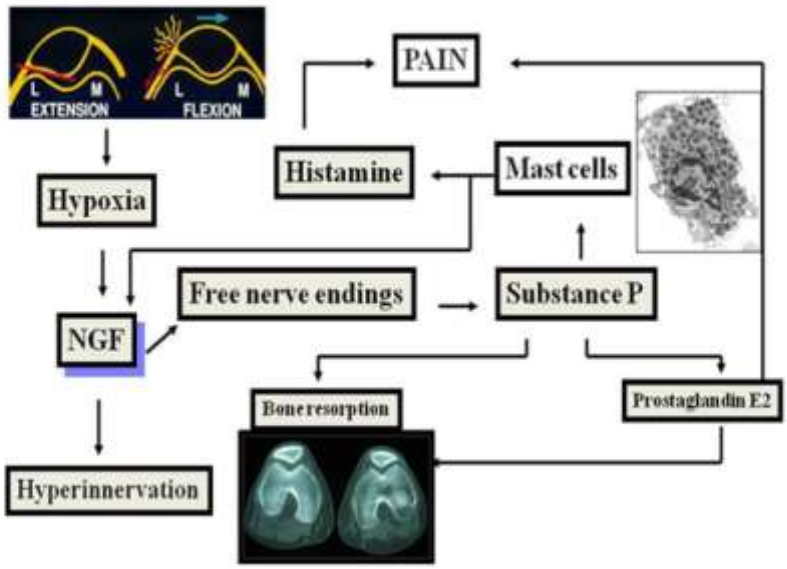

Figure 8. Pathophysiology of anterior knee pain

Woolf [79] described from a clinical point of view four types of pain: (1) Nociceptive pain – transient pain in response to noxious stimulus -, (2) Homeostatic pain – pain that promotes the healing of injuried tissue, that is the cascade of events that participate in the re-establishment of homeostasis -, (3) Neuropathic pain – spontaneous pain and hypersensitivity to stimulus in association with damage of the nervous system-, and (4) Functional pain – pain resulting from abnormal central processing of normal input. Homeostatic pain may include specific symptoms such as allodynia – pain due to stimulus that does not normally provoke pain – and hyperalgesia – a heightened

response to a stimulus that is normally painful -. The phenomenon of rest pain in PFPS ("movie sign") might be an example of allodynia, that is, pain arsing from non-nociceptive afferent activity due to central sensitization and can be induced by ischemia [42]. All these mechanisms are involved in the pathophysiology of pain in PFPS.

CLINICAL RELEVANCE

Anterior knee pain depends not only on mechanical factors, but also on neural factors that are involved in this process. Our findings provide support for the clinical observation that lateral retinaculae play an important role in anterior knee pain syndrome. The resolution of pain by realignment surgery, as we have seen in our series [53], does not necessarily mean that PFM caused theses symptoms. We believe that pain relief after realignment surgery may be attributed in part to dennervation. In the same sense, Vega and colleagues [74] in 2006, described electrosurgical arthroscopic patellar dennervation for the treatment of patients with intractable anterior knee pain and no or minimal malalignment.

Moreover, realignment surgery would not only achieve the effect of denervation mentioned above, but it would also eliminate the tensile and compressive forces that are produced in the lateral retinaculum with knee flexo-extension, that stimulate free nerve endings (a type of nociceptor) [32], and would break the ischemia – hyperinnervation – pain circle.

If the "neural model" of anterior knee pain proves to have certain validity, it would lead in many cases to therapeutic recommendations to alleviate pain more effective and safer than the attempts to correct "malalignment". Thus, specific unloading, a selective pharmaceutical approach, that is to say medications that affect neural pain transmission (eg, drug inhibitors of synthesis and release of SP, or SP receptor antagonists), could be of interest in the treatment of pain in these patients. Finally, if we demonstrate that regional anoxia plays a key role in the genesis of pain, topical periferic vasorelaxant drugs could also be of special interest in the treatment of pain in these patients as well as protecting the knees from decrease in blood flow by means of limitations in time spent with knee in flexion as well as protecting the knees

from a cold environment. Moreover, ice application in these patients may cause increasing of symptoms due to a significant diminution of blood flow following it.

We are now at a turning point. Nowadays, medicine in its entirety is being re-assessed at sub-cellular level, and this is precisely the line of thought we are following in the approach to PFPS. Still to be seen are the implications that this change of mentality will have in the treatment of PFPS in the future, but we are sure that these new currents of thought will open for us the doors to new and exciting perspectives that could potentially revolutionize the management of this troublesome pathologic condition in the new millennium we have just entered. Clearly, we are only at the beginning of the road that will lead to understanding where anterior knee pain comes from.

CONCLUSIONS

We have demonstrated a neuroanatomical basis for PFPS in the young patient and the clinical observation that the lateral retinaculum may have a key role in the origin of this pain. Our findings, however, do not preclude the possibility of pain arising in other anatomical structures.

We hypothesize that periodic short episodes of ischemia could be implicated in the pathogenesis of anterior knee pain by triggering neural proliferation of nociceptive axons (SP positive nerves), mainly in a perivascular location. Our findings are in line with the homeostasis perspective proposed by Dye. We believe that loss of vascular homeostasis in the knee region (e.g. hypervascularity, ischemia, osseous hypertension) may be associated with PFPS. Moreover, we believe that instability in patients with PFPS can be explained, at least in part, because of the damage of nerves of the lateral retinaculum which can be related with proprioception.

SUMMARY

We review the development in the field of pathophysiology of anterior knee pain in the young patient to its current status. Emphasis is placed on newer findings. We have developed what we call the *"Neural Model"* as an explanation for the genesis of anterior

knee pain. According to our studies we hypothesize that periodic short episodes of ischemia into the lateral retinaculum could be implicated in the pathogenesis of anterior knee pain, at least in a subgroup of anterior knee pain patients, by triggering neural proliferation of nociceptive axons (substance P positive nerves), mainly in a perivascular location. Our findings are compatible with the tissue homeostasis theory widely accepted currently to explain the genesis of anterior knee pain. If the *"neural model"* of anterior knee pain proves to have certain validity, it would lead in many cases to therapeutic recommendations to alleviate pain more effective and safer than the attempts to correct *"malalignment"*.

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