Towards a Better Understanding of Anterior Knee Pain

Don´t Forget to Look Up

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"That those who know her, know her less, the nearer her they get"
Emily Elizabeth Dickinson

1. Introduction

Anterior knee pain (AKP), referred to as chronic pain perceived in the anterior aspect of the knee following exclusion of other objective causes of pain, is one of the most common and most challenging knee problems to treat. So, in reality it is a diagnosis of exclusion. It affects physically active individuals between the ages of 15 and 30, females being more likely to develop it. These patients often also tend to report instability of the knee that typically occurs going up or down stairs or on an incline. Besides pain and giving way, these patients also show a different amount of chronic disability, some of them are severely impaired, while others only have a slight disability.[1] AKP is typically caused and aggravated by ascending or descending stairs, squatting, kneeling, using high-heeled shoes and sitting with flexed knees for prolonged periods of time ("movie sign"). Therefore, it is likely that AKP patients are prone to develop avoiding behaviours that may worsen their disability. It causes limitation from participation in sports, sick leave, and generally a reduced quality of life.

However, this diagnosis is really an admission of our ignorance. Currently, in spite of its high incidence and abundance of clinical and basic science research, we really do not know what is causing the pain and disability in these patients. It is generally agreed that many factors may lead to AKP (multifactorial aetiology), but these factors are still not well understood. This could be the reason of unpredictable results after the treatment of this condition. The objective of this paper is to present a complete picture of the AKP patient based on the experience of the author.

2. Structural Anomalies Cannot Fully Account for Pain and Disability in AKP Patients

Nowadays, standard practice for the orthopaedic surgeon is based on biomedical treatment approaches that target the correction of structural abnormalities surgically. Of course, there are patients in whom structural anomalies are the primary cause of their pain, but they represent in

[1] The World Health Organization defines disability as a limitation of function that compromises an individual's ability to perform an activity within the range considered normal.

my clinical practice a small percentage of all patients with AKP. In the vast majority of AKP patients there is a poor correlation between structural alterations of the patellofemoral joint (v. gr. lateral patellar subluxation or patellar tilt) with pain and disability. Moreover, in some cases, important anatomic alterations (v. gr. severe patellar chondropathy or severe patellofemoral malalignment -PFM-) are painless and do not cause disability. In fact, there is consensus about the fact that structural damage of articular cartilage does not always result in AKP although a subset of patients with chondral lesions may have a component of their pain related to that lesion **[1]**. Interestingly, we have seen postoperative PFM at long-term follow-up after Insall's realignment surgery in almost 57% of the patients of our series **[2]**. Nonetheless, we have not found, at long-term follow-up, a relation between the result, satisfactory or non-satisfactory, and the presence or absence of this postoperative PFM. In my clinical practice (1) the worst cases of AKP patients are those secondary to surgeries oriented towards the correction of structural anomalies; and (2) the vast majority of AKP patients have minimal structural anomalies. Of course, there are AKP patients in whom we can demonstrate a relationship between proximal hip muscle weakness and pain **[3]**. These patients respond favorably to an exercise program specifically targeting core stability. These patients have a lateral patella subluxation as the result of the femur rotating underneath the patella in the transverse plane that can result in genu valgum, an increase in the dynamic Q angle, and greater lateral forces acting on the patella. In these cases the key treatment approach is based in a biomedical model.

3. Is the Problem in the Psyche?

Often, there is a mismatch between what we find on clinical examination and the amount of pain and disability. This situation can be frustrating for both patients and the orthopaedic surgeon. Moreover, many but not all patients have a reduction in pain threshold. Therefore, in many cases the orthopaedic surgeon might suspect nothing is really wrong and therefore the problem must be in the psyche. Our multidisciplinary research group did an indepth study about the influence of psychological factors in pain and disability in AKP patients. In this sense, we have performed a cross-sectional study in 97 AKP patients **[4]** and a longitudinal study (level of evidence I) in 54 patients **[5]** to analyze the post-treatment changes in psychological factors and their association with the final pain and disability. Obviously, according to our studies, psychological factors play an important role in pain and disability, but we must not forget that AKP patients have a real neuroanatomic basis for the pain. Psychological factors are only one part of the puzzle.

4. What is the Origin of Pain in AKP Patients?

The cardinal symptom in AKP patients is the pain. Therefore, the question would be: What is the origin of pain? There are several possibilities: lateral retinaculum, synovium and subchondral bone; all of them are rich innervated structures **[6]**. There are several clinical observations that indicate the focal origin of pain ("tissue damage"). In fact, there is an improvement of pain after these locations are injected with local anesthetics.

We have found nerve ingrowth in the lateral retinaculum of patients with AKP and patellofemoral imbalance **[7]**. This hyperinnervation has a predominant nociceptive component, that is, substance P-immunoreactive nerves and usually adopts a perivascular location **[8]**. Vascular innervation is a factor implicated in the pathophysiology of pain in other orthopedic pathologies such as osteoid osteoma and the lumbar facet syndrome. Finally, we have also seen

neuromas, microneuromas and neural myxoid degeneration **[7, 9]**. Regarding neuromas and microneuromas we have found a clear relationship between them and pain, but not between neural myxoid degeneration and pain. We have demonstrated that hyperinnervation is induced by the release of NGF **[10]**. Moreover, we have seen histologic retinacular changes associated with ischemia in the lateral retinaculum that could explain NGF release. In this sense, we have also found hypervascularization that we interpret as an active response to ischemia **[11]**. We have found higher values in the number of vessels in the lateral retinaculum of patients with severe pain than in those with moderate or light pain. Moreover, as expected, we found a positive linear correlation between number of vessels and nerves. Finally, in our series, we have found VEGF (the most potent angiogenic hypoxia inducible peptide) positivity in endothelial cells, perivascular fibroblasts, wall vessels, perineural shift and inside the axons **[11]**. Immunoblot studies revealed a band at the site of VEGF, that is 21 kD, thicker in cases with severe pain, and hardly expressed in those with light pain **[11]**. We must note that nerve damage occurs diffusely in the affected retinaculum, and a possible consequence of this nerve damage could be an altered proprioceptive innervation. 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 AKP 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 the ascendent proprioception pathway or a decrease of healthy nerve fibers capable of transmitting proprioceptory stimuli.

Moreover, we have seen hyperinnervation predominantly of free nerve endings that could be involved in the mechanism of pain in the infrapatellar fat pad adjacent to the inferior pole of the patella, in patients with chronic patellar tendinopathy **[12]**. Moreover, we have seen pathologic neural changes such as free myelinated nerve fibers showing a histological pattern of "nerve sprouting", increased vascular innervation, and neuroma-like formations that could also be involved in the genesis of pain **[12]**.

Finally, subchondral patellar bone could be another source of pain due to its rich nerve supply **[13]**. These intraosseous nerves could relay nociceptive information as a result of mechanical stimulation.

5. What is Causing the Pain?

The crucial question would be: What is causing the pain? There is consensus about **[1]**: (1) patellofemoral imbalance (v.gr. imbalance due to medial patellar instability secondary to lateral retinaculum release, imbalance due to multidirectional instability, or imbalance due to a retracted lateral retinaculum) may cause pain by virtue of cyclical soft tissue stretching and/or bone focal overload; (2) loss of vascular homeostasis (v.gr. hypervascularization, ischemia or osseous hypertension) may also be associated with AKP and could be secondary to patellofemoral imbalance or secondary to a direct traumatism; and (3) focal supraphysiological loading or overuse, that is, cyclical overload of soft tissue or bony areas may explain pain in some patients (Dye´s theory of envelope of load acceptance) **[14]**.

Bone overload is a well-know mechanism of pain in AKP patients given that the subchondral bone is a rich innervated structure, and these nerves could relay nociceptive information as a result of mechanical stimulation. But the question is: What is causing the osseous overload in AKP patients? The answer will be given by biomechanics. Our

multidisciplinary research group has a lot of experience with kinetic and kinematic analysis in this group of patients[2]. In the young patient with AKP we have observed like other authors a significant reduction in the knee extensor moment (that is suggestive of quadriceps avoidance gait pattern) while going down stairs compared to a healthy control group **[2]**. This could be a primary compensatory defense strategy used by patients with AKP to minimize pain aggravation during walking down stairs. The reduction of the knee extensor moment, with the subsequent smaller quadriceps contraction, will cause a decrease of the PFJRF and a decrease of the loading of the PFJ while going down stairs. However, this entails the loss of quadriceps absorption role and therefore a greater shock absorption through the bone and cartilage of the tibiofemoral joint that could explain tibiofemoral pain in AKP patients. Moreover, giving way of the knee in AKP patients could also be the result of reflex inhibition of the quadriceps muscle secondary to pain, effusion or deconditioning. The increment of the knee abduction moment observed in some AKP patients could also explain tibiofemoral pain. The knee extension gait pattern observed in some patients with AKP could also explain tibiofemoral pain, due to the increment of the vertical heel contact force **[15]**. Finally, this extension gait pattern could also explain the popliteal knee pain in these patients given that the posterior muscles work in a chronic manner in an elongated eccentric condition; this situation could be responsible for the posterior knee pain. The mechanical stimulation of patellar intraosseous nerves could also be due to the increment of intraosseous pressure (intraosseous edema) or the increment of the subchondral bone pressure (due to failure of energy absorption of the articular cartilage secondary to the decrease of the contact area –patellofemoral malalignment- or secondary to chondral damage).

We believe that hypoxia plays a key role in the genesis of AKP **[11]**. It has been reported that peripheral nervous system hypoxia can trigger synthesis by neurons of VEGF and NGF. VEGF induces hypervascularization. NGF stimulates neural sprouting and hastens neural proliferation in vessel walls, and this is precisely the pattern of hyperinnervation that is seen in the lateral retinaculum of patients with painful patellofemoral imbalance. Basing ourselves on our data we hypothesize that episodes of temporal tissular ischemia, maybe due to a mechanism of vascular torsion or vascular bending, secondary to medial traction over a retracted lateral retinaculum due to patellofemoral imbalance, could trigger release of NGF. Once NGF is present in the tissues, it induces hyperinnervation, and substance P release by free nerve endings. Substance P stimulates mastocytes which can liberate NGF and nonneurogenic pain mediators such as histamine. Substance P enhances the release of prostaglandin E2 that stimulates nociceptors. Finally, substance P and prostaglandin E induce bone resorption which can explain the osteoporosis associated in some cases of AKP. In summary, we believe that patellofemoral imbalance produces a favorable environment for the genesis of pain and neural damage is the provoking or triggering factor. Obviously, this is only one part of the puzzle.

6. Can Pain Explain Disability?

Another important complaint in AKP patients is disability. There is a generalized belief that pain is the major cause of disability and that the degree of pain determines the actual degree of disability. This could be true in acute pain. For example, a patient with an acute patellar dislocation experiences acute pain limiting his/her mobility and disabling him/her for

[2] We perform the stair descent test. During stair descent there is an increment of the patellofemoral joint reaction force (PFJRF) eight times greater compared to level walking. Therefore, stair descent can be demanding enough from a biomechanical standpoint, not only to aggravate pain in those patients with AKP, but also to provoke it.

his/her ordinary activities. However, it is increasingly evident that disability in chronic pain is poorly correlated with the severity of pain. As other authors we have observed that AKP patients show different degrees of disability in their everyday life, regardless of how intense the pain is. Some patients with a lot of pain show mild disability, while others with much less pain show great disability. In a preliminary cross sectional study performed by our multidisciplinary research group, we have found only a moderate correlation between pain and disability, meaning that pain per se is not able to explain all the variability of disability that AKP patients have **[4]**. Moreover, our regression analysis revealed that pain level was not significantly associated with self reported disability. Thus, although chronic pain and disability may be related, they are independent constructs without a complete correlation. Therefore, there must be other factors apart from pain that have an influence on disability. The key question would be: Which factors could have an influence on disability? Maybe psychological factors?

7. Influence of Psychological Factors on Pain and Disability in AKP Patients. Clinical Relevance

Chronic pain, and AKP should not be an exception, cannot be fully understood in terms of the classical biomedical and structural model of disease that equates pain with tissue damage. During the last decades, explanatory models of chronic pain have changed from the biomedical model to the biopsychosocial model, which suggests that a complete understanding of pain require consideration of anatomical, psychological and social factors **[16]**. In the early 1980s, several authors proposed the fear-avoidance model **[17, 18]**. This model of pain suggests that cognitive and emotional processes are crucial contributors to inter-individual differences in the perception and impact of pain. It establishes two ways to cope with pain depending on how the patients interpret the painful situation. Those patients who interpret pain as not threatening confront the situation maintaining daily activities and are more likely to recover. In contrast, those patients with maladaptative responses including fear of movement, avoidance and hypervigilance tend to result in disuse and disability. This theoretical model was developed in the context of an interdisciplinary back pain clinic and attempted to explain why some patients became chronic back pain sufferers. AKP shares with lumbar pain the fact that there is a very low correlation between symptoms and abnormal findings in imaging studies and also both entities have a tendency to become chronic and develop severe disability. It has recently been suggested that an excessively negative orientation towards pain, that is, the belief that pain will get worse and that one is helpless to deal with it (catastrophization) and kinesiophobia (the belief that movement will create additional injury or re-injury and pain) are related to pain chronification and disability in patients with lumbar pain **[19, 20]**. Based on this observation, we hypothesize that psychological factors (kinesiophobia and catastrophization) are partially responsible for disability and pain chronification in AKP patients. Our objective would be to identify predictors associated with the persistence of pain and disability. From a clinical point of view this topic is relevant because it could help identify therapeutic key targets for additional psycho-educational interventions to improve the results of the traditional treatment.

In a preliminary cross-sectional study, our multidisciplinary research group observed that AKP patients have a high incidence of psychological distress (anxiety and depression), kinesiophobia and catastrophization **[4]**. Although these psychological factors are independent constructs previous investigations in chronic pain patients have shown that they are intimate correlated with significant overlap. Not surprisingly, in our research these variables are moderately correlated among them and also with pain and disability. We have found elevated levels of anxiety and depression in patients with AKP. Both anxiety and depression may

amplify the patients´ perception of pain through cognitive processes and also by neurobiological mechanisms. Although psychological distress in AKP patients is more prevalent than in the general population, this appears to be mainly a result of symptom severity and not the cause of pain and disability. However, in the regression model [3] performed in our series only catastrophizing and depression revealed to be independent predictors for pain and disability. Catastrophizing and depression explain 56% of the variance of disability and catastrophizing explained 37% of the variance of pain **[4]**. In our research, kinesiophobia showed a moderate and significant correlation with pain intensity and disability. However, the regression model excluded it as direct predictor for pain and disability. There is some evidence that pain catastrophizing may be considered as a precursor of pain related fear. This may be the reason which explains that the correlation between kinesiophobia and disability disappears when catastrophizing is taken into account. Finally, in our regression model adjusted for sex, age, kinesiophobia, catastrophizing and depression, anxiety also failed to be a significant predictor for pain and disability.

In another study performed by our research group, we tried to investigate the prognostic value of kinesiophobia and catastrophizing cognitions in the clinical results after treatment in AKP patients **[5]**. We conducted a prospective cohort study (level of evidence I for prognosis) in a sample of 54 AKP patients. Interestingly, after treatment both kinesiophobia and catastrophizing scores decreased. The amount of reduction in catastrophizing strongly correlated with the improvement of functional ability in patients after treatment (r 0.7 $p<0.001$). The reduction in kinesiophobia also gave significant correlation, however this association revealed to be only moderate (r 0.4 $p<0.001$). These results strongly support the notion that maladaptative cognitions influence the clinical course and response to treatment in AKP patients.

In addition to patients' beliefs and attitudes towards pain, recent research has been focused on our own pain beliefs and attitudes towards pain as clinicians. The recommendations that orthopaedic surgeon gives to their patients may have a positive or negative impact on the clinical course of AKP by modifying or reinforcing the patients' attitudes and beliefs. Several studies have shown that the beliefs and attitudes of the clinicians, at least in some cases, contribute to the development of chronic low back pain disability, by reinforcing the perception of crippling disease, developing attitudes of hypervigilance or recommending restriction on ordinary activities **[21]**. As AKP is noted most frequently during activity, such as climbing stairs, running and jumping, it might seem prudent to advise relative rest from such aggravating activities. Finestone et al **[22]** in a study of 59 male army recruits with AKP compared the use of a knee brace versus an elastic sleeve versus no treatment. The no treatment group, who were not allowed to rest or take non-steroidal anti-inflammatory drugs, had less pain ($p = 0.04$) compared to the two groups managed with different types of patellofemoral orthoses. The results suggest that maintenance of normal physical activity aids recovery from AKP. The authors conclude that maintenance of normal activity has a beneficial effect on AKP compared to no treatment and to the use of patellofemoral orthoses (Level II of evidence). In the absence of specific patellar pathology the Evidence Based Medicine advises patients to keep active despite their pain, continue their ordinary activities and stay or early return to work.

Many patients may continue to experience significant pain and disability following a "correct" treatment. One common cause of persistent unexplained pain and poor function after treatment in musculoskeletal conditions are psychological factors. We have found in our

[3] Regression analysis allow us to identify direct mediators and quantify the explained variance.

longitudinal study that high levels of pain catastrophizing have been shown to predict post-treatment pain and poor function in patients with AKP. Depression and catastrophizing are consistently associated with the reported severity of pain, sensitivity to pain, physical disability, and poor treatment outcomes. Therefore, depression and catastrophizing could be considered as therapeutic key targets for additional psycho-educational interventions to improve the results of the traditional treatment. Several studies performed in other chronic pain patients have shown to decrease catastrophizing and fear of movement improve functional status. Indeed, in low back pain patients, several randomized clinical trials have demonstrated similar results between lumbar fusion and cognitive behavioural interventions **[23]**. Consequently, psychological factors could be another part of the puzzle.

8. Conclusion

Unluckily, when many doctors encounter a patient with AKP, they only look at the patient's knee in order to explore and treat it. If we keep in mind that psychological factors modulate the course of illness, we should evaluate these factors and include them in therapeutic targets. If we keep our gaze low so as to only see the knee, we will have fewer opportunities to better understand what is happening and we will be unable to solve the problem. Unfortunately, psychosocial factors are either inadequately addressed or ignored within standard practice. Depression and catastrophizing might all be important therapeutic targets in the multimodal management of AKP patients. Our findings stress the importance of tailoring treatment (personalized treatment or "menu a la carte"): physiotherapy, surgery and psycho-educational interventions.

9. References

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