In Search of the Etiology of Anterior Knee Pain

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2.1 Introduction

Because pain is often the only manifest symptom in patients suffering from anterior knee pain (AKP), an in-depth analysis of this subjective emotion may yield valuable information about this elusive knee condition. This book chapter focuses on pain perception and its mechanisms, physiology, and evolutionary context. In the last 10 years, new insights have contributed to our understanding of pain. Those that focus on pain and the role of homeostatic tissue regulation and are related to AKP will be discussed.

2.2 The Knee Region: A Common Location of Pain

The knee region is a common anatomic location of pain. Pain in this region occurs in persons of all ages. Epidemiological studies found that young persons report regular perception of knee pain when asked,[4,31] and 11% of young children report incidence of everyday knee pain.[23] In adults, knee osteoarthrosis is one of the major causes of chronic pain.[18]

Pain in the knee region also occurs in disparate diagnoses. Bilateral trigger points in this region are mandatory for a diagnosis of fibromyalgia.[42] Pain in the knee region is also the pain that is first and most often reported in decompression sickness.[52]

One reason for the knee's susceptibility to pain may be evolutionary in nature. Millions of years ago, our ancestors who used four limbs for locomotion rose to walk on two legs. To accommodate this change, anatomical and biomechanical adaptation of the knee joint was key; perhaps this was possible only through compromise?

2.3 Pain Classifications

Pain was traditionally classified according to clinical relevance, physiology, or mechanism.[43] The International Association for the Study of Pain (IASP) recently suggested a new system that classifies pain in four main groups[69]:

- *Nociception* (acute pain)
- *Inflammatory pain* (pain during reestablishment of homeostasis)
- *Functional pain* (pain caused by a pathological reorganization of the nervous system)
- *Neuropathic pain* (pain caused by known nerve injury or a disease that is known to cause nerve damage)

This system would classify the pain experienced by patients suffering from AKP into one of two groups: inflammatory pain or functional pain. AKP would normally not be classed as acute pain (nociception) because most studies report a pain duration of 3–6 months for this condition. But Brushoj and colleagues have questioned this consensus and proposed that acute AKP be regarded a subgroup of patellofemoral pain syndrome (PFPS).[11] Also, AKP has seldom been classed as neuropathic pain, and there is little current evidence to do so now. Inclusion criteria for neuropathic pain were recently changed.[41]

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Long-standing chronic pain was traditionally described in terms such as "burning" or "shooting" and often regarded as neuropathic. Involvement of damaged nerve tissue is now a mandatory criterion. Despite this, Jensen et al. hypothesized that a subgroup of AKP patients do suffer from neuropathic pain.[35] Using quantified sensory testing (QST), bedside neurological tests, and case histories, the authors found considerable heterogeneity and overlap in degree and type of nervous system aberration – but no APK patient subgroup was identified as having neuropathic pain.

2.4 Inflammation and Immune Reactions

Distinguishing between inflammatory pain and functional pain is not always easy. The dominant problem is a clear and unambiguous definition of inflammation.

Inflammation is an old term, commonly used and well-known in medical circles, however ill defined.[56] Its main use is for describing sharp and intense reactions to tissue damage – *acute inflammation.* The cardinal signs of inflammation – rubor, tumor, calor, dolor, and function laesa (loss of function) – define what we today recognize as a classic acute inflammatory response; for example, sequelae to traumatic cell injury. These physiological processes give rise to the cardinal signs:

- Increased vascular permeability
- Vasodilation
- Increased granulation tissue
- Initiation of pain
- Reflex muscle inhibition
- Disruption of tissue structure
- Fibro- and metaplasia

But various time-dependent reactions indicate that some inflammatory processes are not of an acute nature. And inflammatory reactions can vary due to the type of stimulus. Three main types occur:

- Exogenous stimuli – for example, microbes
- Endogenous stimuli
- Activation of the adaptive immune system

The most effective initiation of inflammation occurs when microbes (bacteria, viruses, or fungi) gain unwanted access to various areas of our bodies. Cells and molecules of the innate immune system immediately react to these invaders.[1] Activation of cells, molecules, and mediators follows a fairly typical course – *inflammation.* Granulocytes (polymorphonuclear leukocytes) and edema are typical signs of acute inflammation.

Injuries to somatic cells or tissues will also initiate an inflammation. In this second type of inflammation, stimuli are endogenous, as opposed to exogenous stimuli involved in the first type. When cells in our body are damaged, substances and structures that are normally stored inside the cells are released and initiate an inflammatory reaction. The inflammatory cascade of cells, molecules, and mediators resembles – but is not exactly like – the one that occurs in response to an exogenous stimulus. Endogenous stimuli evoke different kinds of mediators, cells, and reactions.

The third type of inflammatory reaction is an activation of the adaptive immune system. The adaptive immune system uses inflammation to kill microbes because it lacks an inherent ability to do so. This interaction between inflammation and immune reaction is typical for the human body.

Once they begin, inflammatory processes follow a predetermined course and cease first when the initial causes are eradicated – healing then ensues. These processes are time dependent. When the stimulus cannot be eliminated, inflammation continues, changing in nature.

Subacute or *chronic inflammation* are terms that have been applied to ongoing inflammation, but likewise, they are ill defined. Tissue that contains increased amounts of monomorphonuclear leukocytes (lymphocytes, monocytes, macrophages, and plasma cells) and fibrosis is undergoing what is commonly known as chronic inflammation. Unfortunately, *chronic* often implies a nonhealing or irreversible condition. Alternatively, *degeneration* has been used to denote the status of tissue with fibrosis and no indications of acute inflammation (mediators, cells, and molecules). Obviously, a new approach for understanding and defining inflammatory reactions is needed.[24,56]

To recap, inflammation is the body's response to injury and homeostatic disturbances. Together with the immune system, inflammation not only senses and reacts to threat and damage but also initiates tissue healing – all critical aspects in maintaining the health of an organism. A growing body of evidence shows that

inflammatory processes are a key factor in homeostatic maintenance, and thus, in what previously were considered to be unavoidable aging processes. Inflammation is nearly always present – recognition of its role in the disease process, in response to and in the initiation of, is growing.[63] Some aspects of inflammatory processes are constantly involved in homeostasis – the adjustments that an organism makes to its physiological processes to maintain internal equilibrium. But some aspects of inflammation also interact with other physiological systems, so a simple model is elusive. Inflammatory processes are involved in nearly all acute and chronic diseases – such as, cancer, AIDS, transplant rejection, obesity, diabetes, musculoskeletal disorders (atherosclerosis, tendon pain, myopathy), Alzheimer's disease, and aging.[24] Future treatment of these diseases will require a deeper understanding of inflammation, and its role in homeostasis of the body. Maybe inflammation should not be understood as being the cause of a disease but as the way the body handles gentle as well as serious hazards to homeostasis?

Inflammation is an umbrella term encompassing reactions at various levels: clinical, physiological, molecular, cellular, and intracellular. During particular tissue damage, some or all of the reactions may occur, and a time-dependent cascade of complex interactions could occur at all levels (Fig. 2.1). After removal of pathogens and dead cells, inflammatory processes act to foster healing of damaged tissue. In other words, phagocytosis and remodeling of new tissues are two ways inflammatory processes help maintain somatic homeostasis.

As mentioned above, activation of the immune system is a pathway that commonly initiates normal inflammatory responses. Many cells express receptors of the innate immune system; examples include macrophages and mast cells, both known to be present during inflammation. When these effector cells are
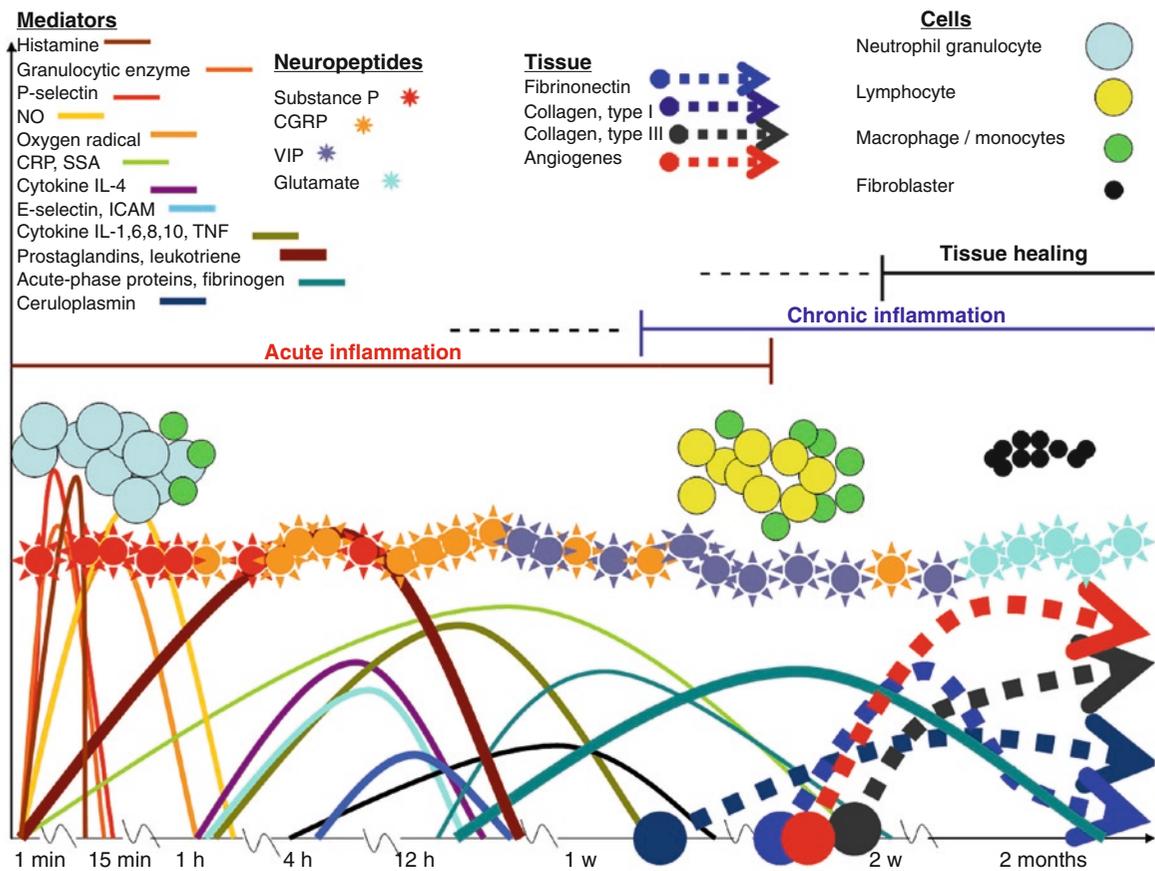
Fig. 2.1 Cells, neuropeptides, and mediators involved in inflammatory processes

activated, they initiate a rapid response marked by release of inflammatory mediators and cytokines (Fig. 2.1). Cytokines (e.g., interleukin-1 [IL-1] and tumor necrosis factor [TNF]) stimulate inflammation.

Inflammation cannot continue unabated without serious hazard to the host. Hence, complex processes have evolved to suppress these responses, repair local damage, and reestablish homeostasis. Immune responses are designed to be self-limited, so processes that initiate resolution are also triggered. For instance, a subset of T-cells promotes resolution of inflammation and tissue repair. As part of the repair process, fibroblasts and other mesenchymal cells produce collagen and other components of the extracellular matrix. These counter-regulatory systems ultimately reestablish homeostasis.

After minor disturbances of homeostasis that only create mild reactions (e.g., syntheses of proteins, increases in metabolism, mild hypoxia, and oxidative stress), some inflammatory reactions will appear but will be scarcely detectable. Previously, despite similarities to inflammation, these mild reactions were seldom recognized as part of inflammation. *Homeostasis* and *immune reactions* describe these physiological processes. So to sum, inflammation is one of the immune system's first responses to injury, infection, or irritation to reestablish homeostasis.

An inflammatory background has been proposed for some chronic diseases, such as cardiovascular disease, diabetes, irritable bowel syndrome (IBS), and cancer. Patients with these diseases present elevated levels of cytokines. Innate immune cells preferentially produce proinflammatory cytokines, which indicates that the immune system has an elevated activation status. Low-grade immune activation occurs during intermittent or chronic inflammation.

Macrophages coordinate innate immune responses; they respond to environmental input signals by initiating resolution of inflammation. These cells play vital homeostatic roles, display remarkable plasticity, and can change their physiology in response to environmental cues. Accordingly, a spectrum of macrophage populations are recognized, among others: classically activated macrophages, wound-healing macrophages, and regulatory macrophages.[44] Macrophages can respond to (1) endogenous stimuli that are generated following injury or infection and (2) signals produced by immune cells. These are examples of the close relationship between various types of inflammation and the immune system.

Per the above, discussing inflammation solely from an acute perspective could lead to false conclusions since inflammation should be viewed as a process that ultimately reestablishes homeostasis.[20] But inflammation can have several etiologies, and this fact is poorly recognized, as evinced in the current discussion on whether tendinopathy should be called *tendinitis* or *tendinosis.*

The healing process that begins with an acute inflammation – that is, peripheral sensitization together with release of substances such as histamine, substance P, prostaglandins, calcitonin gene-related peptide (CGRP), nerve growth factor (NGF), and C-reactive proteins (CRP) – in the presence of neutrophil granulocytes and macrophages alters its nature in a matter of hours, days, or weeks. In this later stage, most cells are lymphocytes and monocytes, with vasoactive intestinal polypeptide (VIP) and glutamate being the dominant neuropeptides (Fig. 2.1).[56] Chronic inflammation might also occur without an initial period of acute inflammation.

The initial stimulus determines the ensuing inflammatory cascade. In the last stage, production of collagen and angiogenesis complete the healing process – and the inflammation dissipates. After several months, patients with long-standing Achilles tendon pain, not surprisingly, present increased levels of glutamate and angiogenesis.[3] Problems in comparing results of various studies seem to arise from the *definition of inflammation* used.

The neuronal cholinergic pathway plays a major role in immune reactions. Lately, also nonneuronal cholinergic pathways have been described, an indication of the importance of acetylcholine (ACh) in immune responses and in inflammation. It has previously been reported that stimulation of ACh receptors induce collagen deposition, cell proliferation, inflammatory remodeling, and promote angiogenesis.[25] When Forsgren and colleagues report evidence of both Ach and Ach receptors in chronically painful tendons, this indicates the existence of a nonneuronal cholinergic anti-inflammatory pathway that might be responsible for typical signs of chronic inflammation.

Organs that sustain chronic inflammation sometime present a multifaceted, multilayered response that involves epithelial to mesenchymal transition, fibroblast activation, recruitment of inflammatory cells, and cellular regeneration at sites of damage.[33] This results in a maladaptive accumulation of extracellular matrix, a condition known as fibrosis.

As mentioned before, some of these inflammatory processes may arise despite lack of observable cell death. Also, the nervous system itself is able to initiate inflammatory reactions (neurogenic inflammation). The major role played by peripheral nerves in initiating and terminating inflammatory reactions must not be forgotten.[1]

Tissue remodeling occurs during the regulation of homeostasis. Excluding visible initial acute inflammation, some of the processes described in chronic inflammation are similar to those in homeostasis. Hypoxia and apoptosis are among the most relevant stimuli in muscle and bone tissue remodeling. But no acute inflammatory processes occur in muscle cell regeneration (protein synthesis) or bone remodeling. Apoptosis occurs as a normal component in most tissues and this kind of cell death does not necessarily signify a physiological problem. The apoptotic process gives rise to a large number of signal molecules that affect the behavior of cells. Apoptosis occurs with minimal or no inflammatory response and even stimulates production of anti-inflammatory molecules.[48] By contrast, necrosis initiates a typical inflammatory response. For the sake of clarity, it must be mentioned that apoptosis of osteocytes, which is involved in the modeling and remodeling of bone tissue, induces TNF-alpha activity, a pro-inflammatory cytokine.[39] Again, defining *inflammation* is troublesome.

Pain perception is part of the inflammatory process. It occurs in acute inflammation, in immune reactions, and in chronic inflammation. But the pain mechanisms that underlie inflammation, immune reactions, and homeostasis may differ substantially.[17] Because the role of some inflammatory mediators – prostaglandin E (PGE), bradykinin, substance P, adenosine triphosphate (ATP), IL-6, TNF – includes triggering pain signals, pain could be considered a homeostatic emotion that facilitates regulation of homeostasis.[17]

Apart from pain stimulation, substance P induces primarily vasodilation and increased levels are correlated to inflammatory reactions. Increased levels of substance P containing nerves have been found in the lateral retinaculum in AKP patients.[54] This suggests an inflammatory process in the knee. Since increased levels of substance P are found in chronic inflammatory diseases like rheumatoid arthritis and Mb Crohn, type of inflammation in AKP is a matter of debate.

2.5 Pain Mechanisms: Peripheral and Central Sensitization, Allodynia, and Hyperalgesia

The classical Cartesian view of pain is that of a homogeneous sensory entity, mediated by a specialized high threshold sensory system that extends from the periphery through the spinal cord, brain stem, and thalamus to the cerebral cortex. But multiple mechanisms that were detected in the nervous system responsible for pain of different etiologies challenge this view. Pain is a subjective experience, it is highly complex, and it is related to nociceptive input in a nonlinear fashion – but despite this, significant pro-and anti-nociceptive modulations affect the perception of this phenomenon.[8]

When pain transforms from an acute (an alarm signal) to a chronic state (a sustained challenge), sections of the nervous system (peripheral nociceptors and neurons in the dorsal horn and various areas of the brain) reorganize. Furthermore, this reorganization continues in the chronic state and has an impact on which signals reach the cortex and are recognized as pain.[5] Apart from pain's influence on cortical functions, continuous reorganization of the supraspinal brain areas responsible for descending modulations of pain occurs. Although unrecognized, descending modulation of afferent signals within the nociceptive pathways is continuous since ongoing afferent action potentials are essential to homeostatic regulation. Normally, descending modulation of afferent impulses in nociceptive pathways prevents all perception of pain – afferent impulses are transmitted from the periphery to higher levels but stop short of the cortical areas of the brain. The exception is when pain is needed to regulate homeostasis.[17]

Perception of acute pain (*nociception*) caused by a noxious stimulus is mediated by a specialized high-threshold sensory system – the nociceptive system. To prevent tissue damage, learned behavior associates certain categories of stimuli with danger that must be avoided. Noxious stimuli are linked with an intense, unpleasant sensation. Accordingly, pain is multidimensional, with sensory, cognitive, and emotional aspects. The sensation generated by acute pain must be so strong that immediate attention is required.

If tissue damage occurs despite the nociceptive defensive system, the body's imperative shifts from protecting against noxious, potentially damaging stimuli to promoting healing of the injured tissue (homeostasis). Pain during inflammatory processes – *inflammatory pain* per

Woolf's definition – is designed to accomplish this goal.[69] In this state, sensitivity (peripheral and central sensitization) increases so that stimulation of the affected area, which would normally not cause pain, now does. As a result, contact with or movement of the injured part is avoided until repair is complete, minimizing further damage. Inflammatory pain typically decreases as damage and inflammatory responses resolve.[69]

In the absence of acute tissue injury, evoked pain may arise from a low-intensity, normally innocuous stimulus, such as a light touch to the skin (mechanical receptors), or it may be an exaggerated and prolonged response to a noxious stimulus. The first condition is *allodynia* and the latter *hyperalgesia.* Allodynia is suggested to be the pain mechanism behind delayed onset muscle soreness (DOMS),[65] and perhaps represents a lower degree of alertness since this pain is not a true alarm signal. The heightened sensitivity of the nervous system that develops during prolonged inflammation can lead to pain onset in the absence of peripheral noxious stimuli (i.e., mechanical allodynia). Two major challenges in pain management are to:

- Identify the mechanisms – peripheral or central plasticity – responsible for producing allodynia and hyperalgesia.
- Find a means of normalizing sensitivity and preventing the changes from becoming established.

2.6 Hypoxia and Allodynia

Sometimes, mechanical allodynia is the best way for the human body to signal pain or discomfort. It is important to understand why this is so. For instance, what homeostatic problem does *the emotion of pain* signal in AKP? Perhaps bone tissue hypoxia.[47,53] And in a sprained ankle, what homeostatic problem does *the perception of pain* signal? Most likely acute tissue damage and acute inflammation.

Mechanical allodynia implies that although homeostasis is suboptimal, no acute threatening event is present, while in acute inflammation, the tissue must not be used or loaded, and high threshold nociceptors are sensitized to transmit this information.

Normally, long-standing, continuous C-fiber activity causes allodynia.[5] This continuous C-fiber activity could be a result of:

- Afferent activity starting as action potentials in nociceptors that eventually become sensitized (peripheral sensitization)

- Chemical stimuli, as in a hypoxic state[60]
- Free polymodal nerve endings that react to several stimuli

Some somatic cells – such as neurons and heart muscle cells – depend exclusively on aerobic metabolism. A short period without oxygen could be disastrous. Other cells – such as leucocytes and erythrocytes – depend exclusively on anaerobic energy production. Muscle cells are capable of anaerobic metabolism for some time. For a few minutes, type II cells can produce ATP in the absence of oxygen.

Bone cells also depend exclusively on aerobic energy production, but they are able to sustain hypoxia for hours during surgery. What impact this might have in the long term is still unknown. Hypoxia in bone tissue has been reported to cause stress fracture,[50] osteoarthrosis,[16] osteoporosis,[51] and AKP.[46,53] It is possible that these diagnoses share the same pain mechanism – mechanical allodynia caused by long-standing afferent signals transmitted in response to chemical stimuli during hypoxia.

On the other hand, intermittent hypoxia is considered one of the most important stimuli in bone remodeling. The Gross and colleagues studies have shown that disuse induces osteocyte hypoxia and that bone hyperemia is locally mediated and precedes onset of disuse-induced intracortical resorption.[29,30] Thus, the same stimulus – hypoxia – initiates bone-cell remodeling *and* causes bone-cell death. The parameters (intensity, duration) for the different reactions are still unknown.

As global regulators of oxygen homeostasis, hypoxia-inducible factors (HIFs) facilitate oxygen delivery *and* adaptations to oxygen deprivation by regulating angiogenesis, erythropoiesis, anaerobic glycolysis, and cellular proliferation (collagen I) and apoptosis.[66] And although HIF signaling appears to play a pivotal role in inflammation,[33] the functional role of HIF in chronic disease conditions is not well understood.

2.7 Bone Tissue, Blood Flow, and Hypoxia

Cardiovascular disease and osteoporosis are major public health problems that frequently coexist and account for significant morbidity and mortality in the aging population. Bone and vascular tissue share

similar pathological features, and accumulating evidence indicates a pathophysiological link between osteoporosis and cardiovascular disease. An age-independent association between progressive atherosclerotic calcification and bone loss has been observed, as has an association between low bone mineral density and mortality due to stroke and cardiovascular disease.[67]

Atherosclerotic calcification is a regulated process with many cellular mechanisms similar to bone formation and resorption. In osteoporosis – as in atherosclerosis – excess lipids accumulate beneath the vascular intima and perivascular area in bones. In the biology of atherosclerosis, inflammation and oxidative stress play a key role – markers of inflammation are increased and correlate with the severity of the atherosclerotic process.[40] The vascular inflammatory response is a complex process that leads to thrombosis, hypoxia, angiogenesis, neointimal thickening, and atherosclerosis. Changes in bone metabolism in patients with AKP suggest an association between hypoxia, bone metabolism, and pain.[12,46,53]

Basic knowledge of how blood flow – and oxygen delivery – is regulated in bone tissue is limited. Because the role of central and peripheral mechanisms in the regulation of blood flow is unknown, the cause of reduced blood flow in bone is also unknown. Shim and Peterson observed that the most potent regulator of bone blood flow in rabbits is the metabolic control mechanism.[59] Blood flow appears to be closely related to oxygen and carbon dioxide tension, pH, and acid metabolites in blood. But in some human bones, a specific mechanism was found to regulate blood flow. For instance, in adults, most of the blood supply to the head of the femur is derived from retinacular vessels on the posterolateral surface of the femoral neck and arise from the medial femoral circumflex artery.[6] This circumstance explains why blood flow to the caput femoris is sensitive to rotation of the femur.

Brookes and Revell suggested that since aging is accompanied by marrow ischemia, periosteal vessels are increasingly responsible for blood supply to the cortex.[10] So the direction of blood flow in long bones could change during senescence. In the elderly, overall vascular patterns in irregular and flat bones vary substantially from the vascular organization of long bones in young persons – young long bones lack the high degree of periosteal blood supply found in older bones.

The patellar bone is situated anterior to the femur in the knee region. Superficially, it comprises a thin layer of cortical bone that surrounds a center composed of trabecular bone. The patella has no bone marrow cavity. Intraosseous vessels in the patellar bone are encased in rigid, unyielding bony cylinders. Five to six main arteries enter the patellar rete and form an arterial circle. These arteries also supply the distal end of the femur and the proximal region of the tibia. Anatomically, they are entirely responsible for arterial blood supply throughout the knee joint.[38] The pain in AKP may be diffuse in character and located in the anterior portion of the knee. Since arterial supply is the same for all bony parts of the knee joint, a peripatellar pain location does not contradict a hypoxic etiology.

2.8 Muscle Activity and Reactive Blood Flow in Bone

An important function of muscles is their role as blood pumps.[62] Wang and colleagues[64] showed that impaired venous circulation reduced interstitial blood flow in bone. Since muscle contractions pump venous blood, it is reasonable to suppose that a long-term reduction or cessation of muscle contractions could cause venous congestion in bones.

Physical exercise appears to increase blood flow to bones, but study results are so far uneven and stem mostly from animal research.[2] Kalliokoski and colleagues reported that *muscle exercise hyperemia* is more widespread if extended periods of muscle work occur at a level where aerobic metabolism is the primary source of energy.[36] The Gross and colleagues[28] study on dogs running on a treadmill found vascular constriction in bone and vasodilation in adjacent muscles.

Marked variations in measured rates of bone blood flow possibly reflect differing metabolic demands of various bone regions. Colleran and colleagues[15] suggested that the inability to precisely regulate blood flow makes bone tissue more susceptible to fluid shifts, which might play a functional role as a stimulus for skeletal remodeling. In muscle tissue, local hypoxia is known to be vital for peripheral blood flow, even though most details of this process are still unknown. Hypoxia is also a possible regulator of microcirculation in bone tissue, but this has not yet been studied in humans.

We have recently found (unpublished) that patellar bone blood flow is influenced by the type of muscle contractions that occur in the surrounding muscle compartments (m. Vastus lateralis). Bone reactive hyperemia was greater after anaerobic muscle work than after aerobic work. This finding supports the Utah Paradigm, which proposes that muscle contractions are key stimuli for bone health.[26]

2.9 Functional Pain

Woolf proposed a new mechanism-based pain classification.[69] As mentioned, AKP is probably best classified as inflammatory pain or functional pain. Although inflammatory and functional pains have different etiologies, they share some characteristics: (1) the pain may arise spontaneously in the apparent absence of any peripheral stimulus and (2) it may be evoked by stimuli. Evoked pain may arise from a low-intensity, normally innocuous stimulus, such as a light touch to the skin or normal non-recognized afferent homeostatic action potentials.

Functional pain is an evolving concept. No neurologic deficit or peripheral abnormality has been detected in this type of pain – it arises due to abnormal responsiveness or abnormal functioning of the nervous system in which heightened gain or sensitivity of the sensory apparatus amplifies symptoms. Several common diagnoses have features that suggest functional pain[69]:

• Fibromyalgia
• Irritable bowel syndrome (IBS)
• Some forms of noncardiac chest pain
• Tension-type headache
• Low back pain (LBP)
• Temporomandibular dysfunction (TMD)

AKP shares many of the characteristics reported in these chronic pain conditions.

It is not known why the central nervous system in patients with functional pain displays abnormal sensitivity or hyperresponsiveness. Still, functional pain is the result of abnormal central processing of normal input. Several lines of evidence support the concept of an altered pain modulatory system (either a dysfunctional descending inhibition or enhanced descending facilitation) in chronic pain states. Recent studies provide evidence that active afferent inhibition of nociceptive input is one way in which cognition modulates pain perception.[8]

In functional pain diagnoses, pain-related psychiatric comorbidity – such as depression, anxiety, and sleeping disorders – are of interest since cognitive and emotional aspects of pain experience are important. Psychological variables, such as catastrophizing, anxiety, and depression, have been implicated in AKP,[14,34,61,68] raising the suspicion that AKP may have nonorganic causes.

Patients with functional pain undergo a different spectrum of treatment modalities – cognitive behavior therapy (CBT) and anti-depressant medication – than patients with inflammatory pain. This leads to the fundamental issue of whether (1) the descending modulatory system in chronic pain patients is faulty or (2) psychological factors like hypervigilance, catastrophizing, and anxiety hinder these patients from an adequate engagement of pain modulation systems. So, it should not be surprising that patients who have had chronic pain for many years develop depression and a passive attitude.

2.10 Anterior Knee Pain in Children and Adolescents

Nonspecific AKP probably has varying etiologies and thus varying pain mechanisms. In children and adolescents, bone growth in relation to the apophysis can trigger an inflammatory reaction when excess stress is put on a musculotendinous junction adjacent to the apophysis. In the knee region, this reaction can occur at apex patellae (Mb Sinding-Larsen, Johansson) and at tuberositas tibiae (Mb Osgaard-Schlatter).

An acute inflammation may occur in response to too much strain. But even in non-acute periods, apophyses are known to produce feelings of pain or discomfort during stress. Since bone growth is warranted and programmed in this situation, peripheral sensitization is probably not the optimal pain mechanism for regulating homeostasis – allodynia is most likely a better regulator of physical activity. A slightly disturbed homeostasis should not induce alarm signals.

Pain from the patellar tendon after intensive use of m. quadriceps is commonly called jumper's knee – or patellar tendinopathy. This diagnosis refers to an

overuse problem that causes an inflammatory reaction. Although distinguishing clinically between jumper's knee and Mb Sinding-Larsen, Johansson is nearly impossible in adolescents, it is important for choice of treatment regime. Regions of the skeleton that are undergoing growth are by nature weak and vulnerable. In children and adolescents, the apophysis will be weaker than the attached tendons while in adults, bone tissue is better able to withstand impact. Different pain mechanisms in the two conditions are probable.

AKP-related research has studied populations of varying ages. Clinical reports of remission or healing of AKP following conservative treatment are common. But as Kannus and colleagues observed, about 30% of AKP patients still have pain years later.[37] These conflicting opinions might arise because bone growth-related pain diminishes with time and ceases when mature bone is established. If AKP has a different etiology, healing may be time independent.

Dye and colleagues reported that, in the knee region, the anterior synovium, the fat pad, and the joint capsule are most sensitive to nociceptive stimuli.[22] Direct trauma and indirect impacts can cause inflammatory reactions in these structures. In the case of direct trauma, the duration of acute inflammation will be brief. But if hypoxia is the source of the inflammatory reaction, and if the hypoxic state continues, a radically different situation occurs.

Because long-standing hypoxia induces central sensitization, the most obvious symptom would be mechanical allodynia. Clinically, typical findings in AKP are activity-induced pain (climbing stairs) and movie sign pain (sitting with flexed knees for prolonged periods). Mechanical allodynia explains these symptoms well.

Exploring the cause of a hypoxic state is critical for treatment success. Sanchis-Alfonso hypothesized that short, periodic episodes of ischemia in the lateral retinaculum is a probable etiology of AKP.[53] The ischemia could trigger neural proliferation of nociceptive axons (substance P-positive nerves), mainly in a perivascular location. The Näslund and colleagues study on pulsatile blood flow in the patellar bone found that flexing the knee 90° significantly reduced blood flow in AKP patients but not in controls.[47] This decrease in blood flow might explain not only the suggested ischemia but also the increased bone metabolism that several studies report, since short episodes of ischemia trigger bone remodeling.[12,21,46]

Sensitivity to cold surroundings is a common clinical feature in AKP. Ben-Eliyahu reported disturbances in knee skin temperature regulation and Selfe and colleagues suggested a cold test for diagnostic purposes.[7,57,58] This is all compatible with the current theory of tissue homeostasis used to explain the genesis of AKP.[20]

But several factors could have an impact on homeostasis. In adolescence, bone growth is vital and is the most prominent factor regulating homeostasis. In school, youth sit daily for hours with flexed knees. Many adults also spend their working days in a sitting position. Combined with impaired arterial supply to knee bones, these circumstances might prevent time-dependent healing and initiate chronic inflammation.

2.11 Treatment Modalities and Pain-Relieving Mechanisms in Anterior Knee Pain

Conservative treatment is the first choice for dealing with unspecified AKP. But there are many modalities, and no consensus has been reached. A probable pain mechanism – if one could be found – would help determine the best treatment modality.[69] But in lieu of a pain mechanism, the next best course is to retrospectively analyze effects of various treatment regimes to explore possible etiologies and pain mechanisms. The current treatment modalities that are most interesting are discussed below in relation to pain mechanism.

2.11.1 Muscle Exercises

Any treatment regime comprising muscle exercises – straight leg raises (isometric muscle activity), open or closed chain exercises (dynamic muscle activity), hip muscle exercises, or functional exercises for the lower extremities – will increase blood flow to the knee region and help decrease any hypoxia. Pain relief after muscle activity could indicate that hypoxia is the main pain mechanism, especially if movie sign pain is a symptom (see the mechanical allodynia section).

Physical activity is also being increasingly advocated in chronic pain treatment. But explanations of

the exact mechanisms behind treatment effects are sparse. One proposal is the release of endogenous opioids. But production of endogenous opioids increases only when physiological stress is apparent and recognized, and the low amount and intensity of exercises commonly used in AKP regimes make it unlikely that endogenous opioids explain the pain relief experienced after lower extremity exercises.

Increased muscle strength after successful rehabilitation has sometimes been suggested as an explanation of pain relief. But if this were so, pain would also arise due to hypotrophy induced by muscular inactivity, and this has not yet been shown. More likely, muscular defects in AKP patients should be viewed as a *consequence* of pain and muscular inactivity – not a cause.

2.11.2 Sympathetic Blockades

Butler-Manuel successfully used sympathetic blockades to treat AKP patients who presented increased bone metabolism on scintigraphy.[12] With sympathetic-mediated pain, blockades of sympathetic tone not only have pain-relieving effects, but will also increase blood flow and eventually decrease hypoxia.

2.11.3 Nonsteroid Anti-inflammatory Drugs (NSAIDs)

The anti-inflammatory effect of NSAIDs arises from inhibition of prostaglandin synthesis, largely by inhibiting the cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid to prostaglandins. This synthesis usually occurs in the acute phase of an inflammation when arachidonic acid is freed from a phospholipid molecule. Accordingly, NSAIDs decrease pain mostly in the acute phase of inflammation. The Heintjes and colleagues study on unspecified AKP and NSAIDs found such treatment to have questionable effects, which suggests that the pain in AKP is not prostaglandin mediated or caused by acute inflammatory reactions.[32]

2.11.4 Taping

The pain-relieving effect of taping regimes has not yet been satisfactorily explained. Although various taping techniques have been presented, exactly how and where the tape is attached to the patellar bone appears to be less important.[13] It might be that allodynia is inhibited when other afferent stimuli are imposed. The proprioceptive role of the tape touching the skin is one example of increased afferent signals able to inhibit allodynia. Taping might also stimulate tactile C fibers responsible for the sense of well-being.[49]

2.11.5 Knee Braces

Apart from inducing afferent signals through skin stimulation, knee braces may also raise skin temperature in the knee region. Most knee braces for patients with AKP are made of neoprene – a material known to increase skin temperature. Afferent signals transmitting a sense of higher temperature could cause pain reduction via the well-known gate-control theory.

2.11.6 Acupuncture

A systematic review on the quality of randomized controlled trials of nonoperative AKP treatment found acupuncture to have the highest methodology score.[9] Because classic deep acupuncture *and* superficial needling produce the same pain relief, important clues for explaining pain mechanisms should be sought in the CNS.[45] Sandberg and colleagues[55] found that both deep and superficial acupuncture may increase peripheral blood flow, so it is possible that acupuncture normalizes hypoxia and allodynia.

2.11.7 Surgery

Biomechanically, the knee joint is considered to be one of the most complicated joints in our body. Fulkerson proposed that biomechanical abnormalities are responsible for malfunctions of the patellofemoral contact, which then produce irritation and inflammation.[27]

Although surgery has been advocated for correcting malalignment and has been performed when conservative treatment fails, it is now rarely recommended in patients with AKP – especially not in children and adolescents.[19]

After surgery, an immediate pain-relieving effect is often experienced. Several explanations for this pain relief have been proposed. One is that denervation occurring in surgery could be responsible. But surgery nearly always means that physical activity decreases for some time and pain causing activities are avoided. The reactive hyperemia following any surgery in the knee region might also help normalize hypoxia and thus be beneficial.

2.12 Conclusions

In any long-term pain condition, a causal explanation is important to seek. One is that a mild disturbance of homeostasis, so mild that it is clinically undetectable, could signal pain. Pain mechanisms differ depending on onset stimulus, immune reactions, and type of inflammation, so distinguishing possible pain mechanisms is valuable. Analyzing inflammatory mediators and immune cells may reveal meaningful information in the search for a diffuse AKP etiology. Retrospective analyses of prior treatment modalities may also yield important clues. This chapter has argued that hypoxia suits well as an etiological factor in AKP.

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