Pathophysiology of bone pain

A review

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Submitted 00-10-17. Accepted 00-11-02

Bone pain differs in many respects from other types of pain (Mercadante 1997). While skin pain is characterized as sharp, pricking, stabbing or burning, bone pain is frequently perceived as aching. It may be accompanied by referred pain and muscle spasm which hardly ever occur with skin pain. The response to treatment with opioids and prostaglandin inhibitors often differs between skin and bone pain.

The mechanisms of bone pain are obscure in several respects. It is difficult to explain why some disease processes of bone cause pain while others, very similar, do not. It is well known that even the same pathology—e.g., cancer metastases in bone—may give rise to pain at some locations but not in others (Front et al. 1979, Patt 1993).

It may be asked whether the central processing of nociceptive information is different for bone pain. Bone nociception is probably processed by the CNS in a way similar to that in other tissues of the same mesodermal origin as joint and muscle. Of particular interest is the recent finding that a change in CNS behavior (central sensitization) can be seen as a consequence of strong and/or long-lasting nociceptive C-fiber input from skin, joint and muscle (Ma and Woolf 1996). This phenomenon is due to the plasticity of the CNS in the same way as the wind-up phenomenon that gives rise to a gradual increase in dorsal horn neuron activity in response to repetitive stimuli (Mendel and Wall 1965) and frequently outlasts the noxious stimuli in both time and response-amplitude (Woolf 1986, 1996). Furthermore, central sensitization appears as secondary hyperalgesia and allodynia (Woolf 1996)—e.g., drilling a hole in the tibia of the rat results in secondary hyperalgesia and allodynia (Houghton et al. 1997), suggesting central sensitization. Morover, some clinical evidence indicates that central sensitization is involved in human pain mechanisms (Arendt-Nielsen and Petersen-Felix 1995), including bone nociception (Mercadante 1997).

Far more knowledge is available about peripheral mechanisms. Nerves containing nociceptive peptides are particularly interesting in this review. Substance P-immunoreactive fibers were found in human periosteum by Grönblad et al. (1984) and, together with calcitonin gene-related peptide (CGRP)-immunoreactive fibers, were also seen in bone and bone marrow (Bjurholm et al. 1988, Imai et al. 1994, 1997). These peptides were present in nerve fibers and terminals characterized as belonging to types IVa and IVb by means of PGP 9.5 synaptophysin-immunoreactivity. The possible relation between nociception and inflammation has been discussed by Hukkanen et al. (1992). Although SP-containing nerves in healthy subchondral bone may not be nociceptive, similar fibers in bone beneath chondral defects may play a nociceptive role (Fortier and Nixon 1997). Furthermore, it was recently suggested that nerve fibers containing SP and CGRP, found in the proximal sesamoid bone of the horse, are nociceptive (Cornelissen et al. 1998). A recent review describes nerves containing SP and CGRP as sensory and involved in the neurogenic inflammation (Iversen 1998) and inflamed subchondral plate of the patella (Wojtys et al. 1990).

Osteoid osteoma, a very painful bone tumor surrounded by nerves, is of particular interest

Nociceptive agents in bone tissue during different pathological conditions

Nociceptive agent [a]	Conditions	Authors
SP [b]	Neurogenic inflammation	Iversen 1998
SP	Subchondral bone inflammation	Wojtys et al. 1990
SP	Osteoarthritis	Fortier and Nixon 1997
CGRP [c]	Neurogenic inflammation	Iversen 1998
CGRP	Subchondral bone inflammation	Wojtys et al. 1990
PGE_2	Osteomyelitis	Plotquin et al. 1991
PGE_2	Osteoid osteoma	Wold et al. 1988
PGE_2	Osteoblastoma	Wold et al. 1988
Prostaglandins	Bone metastasis	Eisenberg et al. 1994
IL-6 [d]	Bone metastasis	Siris 1997
Histamine	Intraosseous edema	Bennet 1988

[a] These agents are very often correlated to nociception
[b] Substance P
[c] Calcitonin gene-related peptide
[d] Interleukin-1

(O'Connell et al. 1998). Surgically-removed tissue was examined histologically by using a traditional silver staining technique (Esquerdo et al. 1976). Unmyelinated fibers were found in the immediate vicinity as well as separated from blood vessels. To reach the sclerotic region (nidus), primarily thin myelinated (Aδ) fibers were seen to penetrate the bone along vessels (Greco et al. 1988). When the nidus was located in the cortex, the nerve fibers reached the lesion via the haversian perivascular space or from the periosteum. By using polyclonal antibodies to PGE2, S-100 protein and protein gene product 9.5 (PGP 9.5), Hasegawa et al. (1993) characterized the nerve fibers. While the antibodies to S-100 protein bind to myelinated fibers, the antibodies to PGP 9.5 bind to all nerve endings. Nerve fibers positive to PGP 9.5 and S-100 protein were detected around the nidus in most cases and within the nidus in some. A close connection between nerves and blood vessels was seen.

Under normal conditions, sensory fibers are unaffected by sympathetic stimulation. However, in—e.g., arthritis—sensory fibers of the joint may respond to sympathetic activity (Kidd et al. 1996). It is reasonable to assume that the same phenomena are also valid for bone. The presence of adrenergic fibers in the haversian canals (Milgram and Robinson 1965) strengthens this view.

Inflammation

A comparison with inflammation in joints may be relevant since bones and joints have the same mesodermal origin. Hyperalgesia, caused by inflammation, appears to play a crucial role in joint pain (Schaible and Blair 1993). It has been established that the hyperalgesia typically seen in inflammation depends on the presence of prostanoids (Schmidt et al. 1994). Recent findings show that prostaglandins are produced in bone tissue—e.g., in response to mechanical loading. Furthermore, prostaglandins are probably involved in the mechanisms of bone loss seen during inflammation and immobilization (Klein-Nulend et al. 1997). The synthesis of prostaglandins PGE_2, PGI_2 and $PGF_{2\alpha}$ is catalyzed by cyclooxygenase (COX). The production of this enzyme is stimulated by cytokines, growth factors, inflammatory mediators, tumor promoters, and hormones (DeWitt 1991). Two isoenzymes have been identified. COX-1 is permanently present in most tissues. The other form (COX-2) is induced, e.g., during inflammation (Siegle et al. 1998). However, the physiological production of prostaglandins in bone seems to depend on COX-2 (Forwood 1996).

Over all, experimental data suggest that bone can produce prostaglandins, i.e., the conditions for hyperalgesia are present in bone. Recent clinical studies show the importance of prostaglandins in bone pain. Thus, the production of prostaglandin in—e.g., human osteomyelitic bone—has been demonstrated. Plotquin et al. (1991) showed

that PGE_2-production increased by 5–30 times in infected bone. The role of prostaglandins in mediating nociception associated with osteoid osteoma and osteoblastoma has been studied. Compared to normal bone, extracts from homogenized tissue of osteoid osteoma and osteoblastoma showed increased concentrations of PGE_2. Such an increase in prostaglandin production is not seen in giant-cell tumor of bone (Wold et al. 1988). In accordance with these findings, pain is reported only at an advanced stage of giant cell tumor of the bone (Edeiken et al. 1990a). On the other hand, pain is the principal symptom in osteoid osteoma (Esquerdo et al. 1976, Greco et al. 1988, Hasegawa et al. 1993). Typically, nocturnal pain occurs, but is relieved by nonsteroidal anti-inflammatory drugs (NSAIDs).

Prostaglandins also appear to play an important role in pain caused by bone metastases. It has been reported (Eisenberg et al. 1994) that NSAIDs are particularly effective in reducing bone pain caused by bone metastases. Pain caused by cancer metastases has been found to respond also to radiation in doses of 40–50 Gy fractionated at 2 Gy per day (Bagshaw et al. 1992). The radiation is effective in 70%–80% of the cases, and it has been suggested that this is due to inhibition of release of mediators of the inflammatory response (Mercadante 1997). Bisphosphonates, such as etidronate, alendronate and clodronate, inhibit IL-1- and TNF-α-stimulated IL-6 production in some human bone cells (Giuliani et al. 1998). Since pain caused by bone pathology is frequently relieved by bisphosphonates (Siris 1997), it seems reasonable to assume that the pain experienced in this and similar conditions is related to IL-6 and indirectly to prostaglandins.

Pain caused by fractures

A well-known reason for bone pain is fracture caused by trauma. It has also been suggested that small fractures—microfractures—due to mechanical stress can cause pain. Whether microfractures commonly cause bone pain has yet to be established.

Bone fracture healing consists of a series of overlapping events: inflammation, soft callus formation, hard callus formation and remodeling (Soames 1995). During the inflammatory phase, hyperalgesia and pain may well be related to released cytokines, prostanoids, histamine and bradykinin. Secondary mechanical hyperalgesia and allodynia were found after a hole was drilled through the tibia or calcaneus in the rat (Houghton et al. 1997).

Osteophytes and pain in osteoarthrosis are common (Spector et al. 1993). It has been suggested that pain is caused either by stretching of nerve endings in the periosteum or by microfractures in the fragile bone in the spurs (Brandt 1999). A correlation between microfractures and bone pain has been suggested in a series of other clinical conditions. Bone pain frequently seen in Paget's disease (Meunier et al. 1987, Kaplan 1994) is normally reduced within 2 weeks by treatment with calcitonin. The pain reduction lasts for several months and correlates with a reduction in serum alkaline phosphatase and urinary hydroxyproline values. Plicamycin (a cytotoxic antibiotic) also reduces bone pain and bone turnover. Similarly, bisphosphonates reduce bone pain together with reductions in serum concentrations of alkaline phosphatases, urinary excretion of hydroxyproline, pyridinoline and collagen-derived N-telopeptides (Delmas and Meunier 1997). The high bone turnover in Paget's disease may cause fragile bone structure and microfractures, resulting in bone pain.

Bone involvement is common in Gaucher's disease. Three types of pain have been described in patients with Gaucher's disease type I. First, nonspecific mild pain is felt, which is caused by Gaucher cells packing the bone marrow. Secondly, bone infarction causes severe bone pain. This bone crisis subsides within a week or two, but the risk of fracture remains. Finally, vertebral collapse is associated with pain (Edeiken et al. 1990b, Katz et al. 1993a, b).

In 2 patients, transient bone pain was experienced after an intravenous injection of rhG-CSF (recombinant human granulocyte colony-stimulating factor). Simultaneously, an increase in total alkaline phosphatase activity in serum and an increased number of neutrophils were found. Since CSF stimulates the formation of the early osteoclast precursor, increased osteolytic activity can be expected (Fukutani et al. 1989, Froberg et al. 1999). Hence, the

bone pain may be due to transient osteoporosis and microfractures.

Bone lesions caused by mechanical stress were studied by bone scan in 23 ballet dancers (Nussbaum et al. 1988). In 10 of 13 dancers, stress fractures, microfractures of trabeculae with associated bone repair, mostly in the tibia, resulted in pain. Pain was reported by 6 of 19 with stress reactions, areas of accelerated remodeling and resorption of bone, located in the feet. This study clearly shows that not all fractures give rise to pain. The location, size and form of lesion may determine the degree of motion at the site of the injury, which may be of importance for nociception. Fracture seems to be more likely to cause pain than reparatory processes. Microfractures at the origin or insertion of a muscle in the lower extremity have also been found to cause pain which gets worse with physical activity (Mills et al. 1980). Furthermore, in 64 military recruits, 124 sites of stress fractures related to exercise were found. In 26% of the cases, no pain was reported (Groshar et al. 1985). 3 pain-free patients showed abnormal uptake of radioactive isotopes (stress reaction) 7–14 days before the development of pain. This finding indicates that pain is not caused by the fracture per se.

Pain is common in osteoporosis. In a clinical trial (Agnusdei et al. 1989), osteoporosis was treated with placebo or ipriflavone (an isoflavone derivative). In the latter group, restoration of bone mass was accompanied by a significant reduction in pain. Similar results were found when postmenopausal osteoporosis was treated with salmon calcitonin (Tolino et al. 1993). The pain relief paralleled the increase in bone mineral content. Presumably, microfracture is the cause of pain in osteoporosis.

Patients with sclerotic bone metastases and a low incidence of fracture have less frequent pain than those suffering from lytic bone metastasis which results in more fractures (Van Holten-Verzantvoort and Bijvoet 1989). The osteolytic process is due to an uncoupling of bone formation from bone resorption, which frequently results in fractures, hypercalcemia, and pain (Kanis 1995, Berruti et al. 1999). Treatment with pamidronate (Purohit et al. 1994) reduces pain in about half (59%) of those treated. In a review by Hortobagyi et al. (1996), the effect of pamidronate on pain caused by bone metastases seemed to be related to healing or stabilization of the lytic bone lesions. The bisphosphonates affect the osteolytic process by reducing osteoclast activity (Siris 1997). The analgesic effects of pamidronate and clodronate are documented (Fulfaro et al 1998). Pain due to bone metastases from prostatic carcinoma frequently responds to clodronate when given intravenously for 10 days (Creswell et al. 1995). One study (Coindre et al. 1985) concerned patients with sclerotic bone metastases from prostatic carcinoma. 3 patients with osteomalacia and fractures of the neck of the femur differed from the rest in having more intense and persistent pain more often, which suggests that bone pain in patients with prostatic carcinoma was mainly caused by fracture.

Change in intraosseous pressure

Bone exposed to mechanical forces such as bending causes fluid to flow into the canaliculi of the cortical bone, which, as in the dentinal tubules, may stimulate nociceptive nerve endings. Inflammation and other similar pathological processes in bone, which increase the intraosseous pressure, may also cause pain (Bennett 1988).

How mechanical energy is transferred into nervous elements in bone is not well understood, but it has been extensively studied in teeth. The two types of tissues are rather similar, which makes a comparison meaningful; soft tissues and nerves are encased in hard tissue; tubules containing cell processes and fluid are present in both cases (Soames 1995). In the tooth, drilling or rapid drying of exposed dentine with—e.g., blasts of air—mostly produces sharp pain. It has been shown that such procedures induce fluid flow in dentinal tubules (Brännström 1966) which, in turn, causes intradental nerve activity (Närhi and Haegerstam 1983). In clinical studies, such activity has been shown to cause pain (Ahlquist et al. 1984, Fors et al. 1984).

Axon reflex is probably active in bone since various peptides—e.g., SP, CGRP together with VIP—have been found in the nerves of bone (see above). Such peptides are normally related to hyperalgesia and pain in—e.g., the joint (Kidd et al. 1996). To what extent PGI_2 and PGE_2 released by strain (Zaman et al. 1997) contribute to hyperalgesia and bone pain is not known. Pain caused by pulpitis,

however, may be relevant in this context since it has been suggested that a slight increase in intrapulpal pressure due to inflammatory edema stimulates nociceptors (Skidmore 1991) and the same mechanism may be active in bone marrow. In the bone with its rigid walls, neurogenic inflammation and the resulting vasodilatation and edema may increase pressure and cause pain (Pilmore et al. 1998). Neurons are sensitive to pressure to a greater or lesser degree; first, the myelinated fibers are blocked, and then the unmyelinated fibers. Therefore, the clinical consequences should be an increase in sharp pain due to stimulation of sensitized myelinated fibers, followed by a dull pain when the myelinated, but not the unmyelinated, fibers are blocked, and then analgesia, when both types of fibers are blocked. Such a sequence has been seen in pulpitis (Ngassapa 1996). Pain is common in acute osteomyelitis (Norden 1985). As in pulpitis of the tooth, the pain eventually fades away.

Since the trabecular bone is connected with the subperiosteal space via Volkmann's canals, transportation of sterile or infected fluid through these canals may explain the periosteal hyperalgesia. Elevated intraosseous pressure may eventually reach a level when fluid is forced through Volkmann's canals to the subperiosteal space. The result will be a painful separation of the periosteum from the bone (Clawson 1980). On the other hand, if extensive nerve compression is caused, the nerves are blocked (Rydevik 1979) and no pain is felt. In untreated osteomyelitis, local inflammation and pain together with a raised erythrocyte sedimentation rate may occur now and then over several years (Bouvier et al. 1993, Lew and Waldvogel 1997).

Adult patients with thalassemia sometimes have bone pain, which is ascribed to expansile bone marrow processes that increase the intraosseous pressure (Angastiniotis et al. 1998). The severe pain in osteoarthrosis, which typically continues during the night and is relieved by bone drilling (Pedersen et al. 1995), is caused by an increase in intraosseous pressure (Dieppe 1999).

Neoplastic bone lesions may vary from purely lytic lesions to dense areas containing foci of woven bone, cartilaginous and fibrous elements. Fast growing tumors may completely destroy the cortex (Hasegawa et al. 1993, Longo 1994, Krane and Schiller 1994) and cause pain related to high intraosseous pressure. It has been suggested that the bone pain at rest may be due to this mechanism (Chigira et al. 1984). In addition to the mechanical effect of an increase in intraosseous pressure, the inflammation induced by tumor growth contributes to pain (Bruera and Ripamonti 1993).

Impaired circulation

Experimental data suggest that edema caused by inflammation in bone increases intraosseous pressure (Rosier 1993). Even a moderate increase in the pressure in low-compliance compartments, such as teeth and bone, may cause venous occlusion and impair blood flow (Wannfors and Gazelius 1991). Although arterial occlusion results in more severe hypoxia, venous occlusion leads to a moderate reduction in partial oxygen tension in bone (Kiaer et al. 1992). However, when the venous pressure rises to the same level as the arteriolar pressure in a closed system such as bone, the blood supply almost stops (Mankin 1992). Thus ischemia of bone for 3 hours or more causes an inflammatory response (Kalebo et al. 1986). Endothelial cells stimulated by hypoxia produce arachidonic acid metabolites, such as PGD_2, $PGF_{2\alpha}$, PGI_2 and PGE_2, which are involved in hyperalgesia (Michiels et al. 1993). High local levels of histamine are also thought cause intraosseous edema, elevated intraosseous pressure, and pain (Bennett 1988).

During an infection, the blood flow in bone becomes impaired (Norden 1985). Infectious processes may eventually result in thrombosis of small blood vessels. Inflammation with resulting edema increases the intraosseous pressure, with a further reduction in the circulation. However, in the initial phase of an infection and during an exacerbation, blood flow increases, in contrast to the reduced bone blood flow in the inactive phase of the disease (Wannfors and Gazelius 1991). In patients with active Paget's disease of bone, laboratory findings indicate that accelerated bone turnover and increased blood flow to the bone tissue in untreated patients go parallel with bone pain (Wootton et al. 1981, Agnusdei et al. 1992). A substantial increase in alkaline phosphatase is accompanied by doubling of the blood flow. Treatment with calcitonin

reduces the blood flow to normal before any change in alkaline phosphatase is seen. It has been suggested that rapid relief of the bone pain is related to reduction in blood flow. When recruitment of osteoclasts is inhibited by a drug (ipriflavone), serum alkaline phosphatase and urinary hydroxyproline/creatinine excretion are reduced simultaneously with a significant reduction in bone pain (Crisp et al. 1989, Agnusdei et al. 1992). The findings in osteomyelitis and Paget's disease suggest that bone pain can occur together with an increase in intraosseous blood flow.

Osteonecrosis caused by infarction of medullary bone is usually silent. In a more expanded form involving medullary and cortical bone, osteonecrosis is painful. Mankin (1992) has pointed out that thrombotic occlusion of venous drainage increases venous pressure in bone. The resulting reduction in blood supply may cause bone necrosis. The pain is usually mild and diffuse in chronic forms of osteonecrosis, but with large infarcts in Gaucher's disease, hemoglobinopathy and dysbaric conditions, it can be intense (Mankin 1992, Mont et al. 1997).

Severe bone pain is a side-effect of treatment with cyclosporin after organ transplantation (Barbosa et al. 1995). It mainly affects the knees and ankles, is typically of acute onset, episodic in nature, and bilateral. Severe osteoarticular pain of the lower limbs develops in some patients after renal transplantation (Goffin et al. 1993). It frequently occurs when lying down and is usually relieved by sitting up or walking. Since bone pain is relieved by calcium channel inhibitors, and some patients have a coexisting osteonecrosis, the pain may be caused by a vascular mechanism. In 2 patients with bone pain following renal transplantation, edema and avascular necrosis of the bone tissue was seen with MRI (Pilmore et al. 1998).

Sickle cell disease, a genetic disorder, is common in some African areas (Berde and Shapiro 1995). It is caused by a change in shape of the red cells. These cells are less deformable, which hampers their passage through small vessels. The resulting sludging of red cells in vessels frequently causes ischemia or infarction. Such vaso-occlusive episodes are manifested as "crises" or "painful episodes" (Dickerhoff and von Ruecker 1995). The similar location of pain and caisson-induced bone infarcts suggest that infarcts may play a role in production of bone pain (Horvath 1978). Furthermore, focal bone marrow ischemia has also been suggested as the cause of limb pain in patients with dysplastic and proliferative marrow disorders (Vande Berg et al. 1993).

Painless bone conditions

The fact that some bone metastases of cancer cause pain but others do not (Walley and Hager 1995) suggests that local production of pain-modulating agents may be responsible for analgesia in some cases. According to Elhassan et al. (1998), opioids produced in bone tissues are involved in the control of bone formation and in nociception. Rosen and Bar-Shavit 1994) and Rosen et al. (1998) found that osteoblastic cells were able to synthesize proenkephalin m-RNA. Thus enkephalin is also formed in bone. According to these authors, opioids are involved in bone development and remodeling and their production is initiated when rapid growth is required, such as fracture repair. According to Stein (1995), the peripheral antinociceptive effect of opioids is more marked in inflamed tissue, partly because of easier access to peripheral opioid receptors after disruption of perineurium during an inflammation. Moreover, a subpopulation of immune cells in lymph nodes—e.g., memory $CD4^+$ T-cells-produce β-endorphins, which may control pain at the site of inflammation (Sharp and Yaksh 1997).

Conclusion

The purpose of this review was to summarize clinical data on pain caused by various disease processes in bone and to integrate such data with experimental findings of relevant pathophysiological mechanisms. Inflammation seems to play an important role in bone nociception. Some data indicating that inflammatory mediators cause hyperalgesia in bone, as in many other tissues. Pain in primary bone tumors, in lytic metastatic lesions and in Paget's disease is partly due to immune responses but it is uncertain whether this is exclusively by release of substances which stimulate nociceptors directly, or via an initiated inflammation and sub-

sequent hyperalgesia. In several pathological bone conditions, pain is accompanied by fractures. However, the inflammatory component of the early phase of fracture healing and the resulting hyperalgesia are probably important for nociception. A moderate change in intraosseous pressure appears to induce bone pain. A persistent increase in pressure reduces blood supply and blocks the nerve, causing anesthesia. When the intraosseous pressure exceeds a certain level, fluid in the bone enters the subperiosteal space and induces a painful periosteal reaction. In some conditions, bone pain seems to be caused by infarction and ischemia. In others, it seems to be associated with an increase in intraosseous blood flow. The mechanism underlying bone pain caused by a change in blood supply is obscure. The clinical finding that only some bone lesions cause pain can, at least partly, be explained by an opioid mechanism in the affected bone tissue.

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