Skeletal Microdamage: Less about Biomechanics and More about Remodeling

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This is the author's manuscript of the article published in final edited form as: Allen M. R., Burr D.B. (2008). Skeletal microdamage: less about biomechanics and more about remodeling, Clinical Reviews in Bone and Mineral Metabolism, 6(1-2): 24-30. Available from: http://dx.doi.org/10.1007/s12018-008-9015-5

Abstract

The mechanical consequences of skeletal microdamage have been clearly documented using various experimental methods yet recent experiments suggest that physiological levels of microdamage accumulation are not sufficient to compromise the bones' biomechanical properties. While great advances have been made in our understanding of the biomechanical implications of microdamage, less is known concerning the physiological role of microdamage in bone remodeling. Microdamage has been shown to act as a signal for bone remodeling, likely through a disruption of the osteocyte-canalicular network. Interestingly, age-related increases in microdamage are not accompanied by increases in bone remodeling suggesting that the physiological mechanisms which link microdamage and remodeling are compromised with aging.

Key words: microcracks, toughness, targeted remodeling, aging,

Introduction

Microdamage accumulation in bone is a normal physiological event which is the consequence of repeated cycles of loading during activities of daily living (1, 2). Under normal physiological conditions, the microscopic cracks that are formed in bone are arrested by the morphological features and heterogeneous material properties of bone, and then are repaired by bone remodeling. These processes are usually in balance, although under circumstances of aging (3) or suppression of remodeling by pharmaceutical agents (4-6) the balance between microdamage formation and replacement can enter disequilibrium, and damage can accumulate to levels that are significantly higher than in healthy, untreated bone.

What are the biomechanical consequences of microdamage accumulation?

Bone biomechanical properties exist at two hiearchial levels, those of the whole bone (routinely called *structural properties*) and those of the tissue itself (routinely called *material properties*) (7, 8). Structural properties, including ultimate load, stiffness, and work to failure, are dependent on variables such as bone mass, geometry/architecture, and the material properties of the tissue. Material properties, including ultimate stress, modulus, and modulus of toughness, are determined by various components of the mineral (e.g., degree and heterogeneity of mineralization) and organic matrix (e.g., collagen content and extent of cross-linking).

In laboratory studies, it has been shown that the initiation and growth of microscopic cracks reduces the overall strength (9) and stiffness of bone (10). This has often been interpreted as suggesting that microdamage in bone makes it more prone to fracture. Indeed, damage in both biological and non-biological materials is defined by engineers as the loss of stiffness (11, 12), and a common criterion for failure that has been used in

the past is damage equals or exceeds a 30% loss of the original stiffness of the material (13). Yet microdamage is also known to serve as an outlet for energy dissipation by relieving stress (14). If microcracks were prevented from forming, it is likely that bone would fail with less deformation, and in a more brittle fashion. This may be one reason for the longer fatigue life of bone from younger donors than from older donors as younger donors tend to form lots of small microcracks in localized areas rather easily (diffuse damage), whereas older donors relieve stresses by forming fewer but longer linear microcracks (15). The energy dissipation properties of microcrack formation are exemplified by the observation that very tough materials – those that require a lot of energy to break – typically form cracks easily, but prevent their growth through incorporation of materials of varying stiffness within their structure. These contrasting effects of microdamage on biomechanical properties, -- reduction of residual strength and stiffness but enhanced toughness -- derived mainly through ex vivo laboratory experiments, make it difficult to predict the biomechanical implications of microdamage in the living skeleton.

Studies using animal models have explored the relationships between microdamage and biomechanical properties in depth. These experiments have shown that an increased microdamage burden is associated with reduced tissue toughness, but not with alterations in any other biomechanical parameters (4, 5, 16, 17). This modulus of toughness is a reflection of the energy required to cause failure at the material level, and is defined as the total area under the stress-strain curve derived from a mechanical test (8). Cause and effect between microcrack accumulation and reduced toughness has never been demonstrated at the levels to which microdamage can accumulate in the body during normal physiological circumstances, even with suppression of remodeling using pharmaceutical agents. Therefore, it is not clear that microdamage accumulation

in bone under normal physiological circumstances is even a relevant biomechanical concern for living bone.

Suppressing bone remodeling in intact, non-estrogen deficient dogs for one year using doses of bisphosphonates approved by the FDA for treatment of Paget's disease or osteoporosis, and used under other circumstances to prevent bone loss and skeletal metastasis in certain kinds of cancer, allowed a 2- to 4-fold increase in microdamage accumulation in the lumbar vertebrae (5), and a 4- to 7-fold increase in the ribs (17). These early studies used high doses of oral bisphosphonate which were criticized for being 5x higher than those used to treat postmenopausal osteoporosis (PMO). Although the doses were comparable to those used clinically for the treatment of Paget's disease and therefore relevant to human disease, patients with Paget's disease would never take these high doses of bisphosphonates for more than a few months, certainly never for as long as a year, which was the treatment period in these experiments. More recent experiments using lower doses comparable to those used for the treatment of PMO demonstrate conclusively that suppression of remodeling, even at these clinically-relevant lower doses, is associated with a 3- to 4-fold increase in microdamage accumulation in the lumbar vertebrae of non-osteoporotic dogs (4) **(FIG 1)**. Milder suppression of turnover, either using doses of bisphosphonates below the clinical dose equivalent or an FDA approved selective estrogen receptor modulator (SERM – raloxifene) still allowed a significant increase in microdamage accumulation (4, 18). These latter changes occurred with as little as a 20% reduction in turnover rate showing that virtually any reduction in the site-specific rate of remodeling allows microdamage to accumulate.

Whether the level of microdamage accumulation in these experiments alters the mechanical properties of the bone is open to question. While several experiments have shown that animals treated with bisphosphonates have increased microdamage and reduced toughness (4, 5, 16-18), the direct relationship between these changes has yet to be defined. Recent data from the dog model has provided several pieces of evidence suggesting there is not a direct relationship between levels of microdamage produced in vivo and changes in bone toughness. The most convincing evidence of this lack of cause/effect comes from aging dogs. Treatment of dogs which were a year old at the initiation of treatment for either one or three years with saline vehicle (analogous to an aging model) showed an age-related decline in vertebral bone remodeling, an age-related increase in microdamage, yet no age-related difference in vertebral bone toughness (19) **(FIG 2)**. If microdamage were a key contributor to reduced bone toughness, significant differences in toughness should have been noted between these animals of different ages. These data are supported by the general lack of congruence between changes in microdamage and toughness among various bisphosphonate-treatment groups **(FIG 1)**. For example, a 3- to 3.5-fold increase in damage accumulation at doses of bisphosphonates used for osteoporosis is associated with toughness reductions of between 5 and 17%, whereas a ~5-fold increase in damage at the higher doses is associated with toughness reductions in the same range (10-14%) (4, 5). Moreover, these experiments yield a weak, non-significant r^2 value of 0.01 for correlations between microdamage accumulation and toughness **(FIG 3)**. Collectively, these data strongly indicate that factors other than microdamage accumulation are principally responsible for the reductions in toughness reported with bisphosphonate treatment and physiological levels of in vivo microdamage have minimal effect on biomechanics.

What is the role of microdamage in bone remodeling?

Frost originally proposed a link between microcracks and remodeling based on the concept that repairing microdamage would be essential to prevent catastrophic failure of the bone (2). This has been demonstrated several times by different laboratories using different animal models and is now considered an integral component of bone remodeling physiology (20-24) **(FIG 4)**.

The concept of microdamage initiating bone remodeling was first addressed experimentally using a dog limb overloading model (25). This study found that localized regions of bone with higher amounts of microdamage also had higher numbers of resorption cavities yet the association between the two was not explored in detail. Subsequent experiments in which physiological external loads were imparted to induce microdamage in canine forelimbs showed that four days post-loading there was an association between microdamage and resorption spaces that was >40 times higher than would be predicted by chance (26). Although later re-analyses of the data suggested the association to be lower (6x higher association than by chance) but still significant, these data provided strong evidence of a physiological relationship between microdamage and remodeling (27). It remained possible, however, that the microdamage generated by loading preferentially developed in regions undergoing remodeling (28). This alternative hypothesis was tested by comparing levels of microdamage and remodeling eight days after in vivo loading to levels immediately following loading in canine forelimbs (29). The levels of microdamage in both loading groups were significantly higher than in non-loaded limbs while there were higher levels of resorption cavities only in those limbs that had been loaded eight days earlier. A significant number of the resorption cavities were associated with microdamage **(FIG 5)**, providing convincing evidence that microdamage served as an initiator for remodeling.

More recent studies using similar experimental methods in a sheep model have documented temporal loading-induced changes in microdamage and remodeling, showing that both parameters peak and return to control levels at similar times post-loading (30).

While the studies in canine bone provided the foundation for defining the physiological role of microdamage in initiating remodeling, the most convincing studies to show the relationship between microdamage formation and remodeling utilized external fatigue loading in a rat model (31). Rats do not normally undergo intracortical resorption, so the finding of both microdamage and intracortical resorption spaces in the cortex following loading has unequivocally shown the cause/effect relationship between these parameters. Ten days after fatigue loading both microdamage and intracortical resorption spaces were noted in the ulna with preferential location of the remodeling cavities near sites of damage (31). Further proof of a relationship from this experiment comes from the fact that two rats which did not have microdamage following loading also did not have intracortical resorption cavities. Findings of damage and remodeling in the rat model have been shown in subsequent studies by this same group (32) as well as by others (33-35). Recent evidence of loading-induced microdamage and remodeling in mice (36) will likely open the door for future work using transgenic animals to understand the molecular signals connecting microdamage and remodeling.

Additional insight into the relationship between microdamage and remodeling has been gained from the studies using beagle dogs treated with anti-remodeling agents. Dogs treated with anti-remodeling agents (either bisphosphonates or raloxifene) or allowed to naturally age, accumulate significant amounts of microdamage in the ribs and vertebrae; the magnitude of accumulation is inversely correlated to the level of turnover

suppression (4, 5, 16-19, 37). These studies have provided important information concerning the relationship between microdamage and remodeling. Suppression of remodeling leads to reductions in both targeted and non-targeted remodeling (38). Large reductions in remodeling suppression are not essential for accumulation of damage, with turnover suppression of only 20% sufficient for a significant 2-fold increase in vertebral damage accumulation (18). Finally, the increases in microdamage with remodeling suppression is most rapid during the early phase of treatment such that prolonged remodeling suppression does not significantly increase levels of damage beyond those accumulated early in treatment (19). This plateau in damage accumulation is likely explained by other changes associated with prolonged remodeling suppression that limit damage formation such as increased bone mass which reduces localized strains below the damage threshold (39). This would lead to a new equilibrium between damage initiation and remodeling being achieved over time. Such a new equilibrium would be consistent with physiological levels of microdamage not compromising biomechanical integrity.

The idea of targeted remodeling, originally theorized by Frost (2), was put forth as a viable mechanism through which the bone could minimize accumulation of damage and prevent fatigue failure (40). Based on the early data from canine loading experiments, approximately 30% of all remodeling in cortical bone has been suggested to be targeted toward removal of microdamage (29, 41). Whether the remaining 70% is truly random, or whether it is targeted to other areas of bone, for example regions that have high strain, are highly mineralized, or have compromised osteocyte integrity, is unclear (24, 41). Martin has suggested that in a normal, healthy skeleton all cortical bone remodeling is targeted to microdamage (42). Using a mathematical model, he was able to computationally explain how the experimental evidence for targeted remodeling

underestimates the association between microcracks and remodeling cavities because of the 2D assessment of these 3D structures (microcracks). One criticism of the idea that all remodeling serves the purpose of removing microdamage is that remodeling units are typically several millimeters in length (43), thus the need to remove such a large amount of tissue for the sake of removing a single microcrack is difficult to understand. To address this concern, Martin developed a follow-up model showing how this could be reconciled through an osteonal steering mechanism, where remodeling units that are formed and targeted to remove a specific microcrack can then steer their trajectory in order to remodel other nearby cracks (44).

The mechanism(s) through which microdamage signals bone remodeling is not understood although most evidence points to a disruption in the osteocyte/canalicular network. Data from the rat fatigue loading model have shown significantly higher numbers of apoptotic osteocytes near microdamage within the loaded limb compared to the non-loaded limb of the same animal, or sites within the loaded limb that are distant from microdamage (32, 33, 45). Osteocyte apoptosis is elevated as soon as twenty-four hours post-loading, thus preceding the appearance of remodeling cavities, and appears to be coordinated through key regulators of the apoptosis pathway including Bax and Bcl-2 (32, 45). Osteocytes near cracks have increased expression of Bax, a pro-apoptotic signal, while those more distant from microdamage have increased expression of Bcl-2, an anti-apoptotic signal, effectively creating a target for remodeling (45). These data provide intriguing evidence that dying osteocytes signal remodeling to regions of bone containing microdamage. But why do the osteocytes die with fatigue loading? The most prominent hypothesis is that osteocyte processes are physically broken by microdamage, disrupting cell-to-cell communication and fluid flow (20, 23). This is supported by the abundance of evidence showing fluid flow plays a key role in osteocyte

physiology (21, 46, 47) and that both fluid flow (35, 48) and cell process connections (49) are disrupted following fatigue loading. The nature of the cellular and molecular mechanisms underlying damage-related targeted remodeling should be a key focus of future microdamage research.

Aging bone: An exception to the rules of microdamage and remodeling

Age-related changes to bone tissue properties, such as decreased mineralization heterogeneity and increased collagen cross-linking, make the bone more susceptible to microdamage (50). It would be expected that increases in microdamage formation with age would be held in check by remodeling, yet there exists a clear age-associated increase in microdamage accumulation (3, 51-55), indicative of a breakdown in the microdamage-remodeling feedback loop. Bone remodeling tends to increase with age (56) and can be enhanced further with anabolic agents such as parathyroid hormone (57), illustrating that aged bone retains the ability to remodel. This suggests that dysfunction with age is in the signal(s) coming from the damaged regions. One possible explanation is that the signal originating from the tissue surrounding microdamage is compromised with age such that the remodeling units do not recognize the tissue has been damaged. Osteocyte number declines with age (58), and with fewer cells, the strength of the remodeling signal may be diminished. Fewer cells and canaliculi would also reduce the probability of a given crack breaking a sufficient number of osteocyte cell processes to initiate the signal. Another potential explanation could be that the signal for remodeling exists but for some reason is not adequately transmitted to the osteoclasts (or it is delivered but not properly interpreted). Reductions in osteocyte numbers with age, as well as reduced mechanical loads from physical activity, would be expected to reduce fluid flow through the bone which could in turn compromise the dissemination of soluble signals coming from osteocytes. Finally, age-associated changes in osteocyte

gene expression could result in down-regulation of the signal for targeted remodeling. No matter what the dysfunction ultimately turns out to be, the key concept is that by studying this disconnect between microdamage and remodeling with aging we are likely to gain a better understanding of their normal physiological interaction.

Conclusions

Recent data from in vivo experiments provide convincing evidence that physiological levels of microdamage accumulation do not compromise the biomechanical properties of bone. This suggests that in the absence of pathological levels of skeletal damage, the biomechanical implications of microdamage are likely insignificant with respect to fracture risk. The more important role of microdamage in bone physiology appears to be for initiating and targeting of bone remodeling. The intimate link between microdamage and remodeling is clear yet the specifics concerning the mechanisms underlying the signals remain an area for future study.

Figure Legends

Fig 1. Minimal congruence exists between changes in microdamage and toughness. Following one year of treatment, microdamage in the vertebra of beagle dogs is significantly increased in animals treated with bisphosphonates (risedronate (RIS) or alendronate (ALN)) or raloxifene (RAL) compared to vehicle-treated animals. The level of toughness reductions compared to vehicle controls, none of which were statistically significant, showed little relation to the level of microdamage increase. Data adapted from (4, 18).

Fig 2. Physiological increases in microdamage through aging-related reductions in bone remodeling are not associated with compromised bone toughness. Untreated dogs,

assessed at two- and four-years of age, showed significant (* $p < 0.05$) age-related reductions in trabecular bone remodeling (activation frequency) and age-related increases in microdamage accumulation (microcrack density) of the vertebra. Despite over a 3-fold increase in microdamage with age, modulus of toughness, the energy absorption capacity of the bone tissue, was similar between the two groups suggesting that physiological increases in microdamage do not play a prominent role in altering bone toughness. Data adapted from (19).

Fig 3. Lack of correlation between microdamage and toughness. The level of microdamage accumulation (crack surface density) within trabecular bone of the vertebra from animals treated for 1 or 3 years with various anti-remodeling agents (alendronate, risedronate, or raloxifene) or vehicle controls showed no relationship to toughness ($r^2 = 0.01$). Data adapted from (4, 18, 19).

Fig 4. Bone remodeling, initiated by a microcrack and the associated osteocyte apoptosis. Reprinted from (22) with permission from publisher.

Fig 5. Microdamage as a target for bone remodeling. Photomicrograph depicts a basic remodeling unit (*) within cortical bone traveling toward a microcrack (arrowhead).

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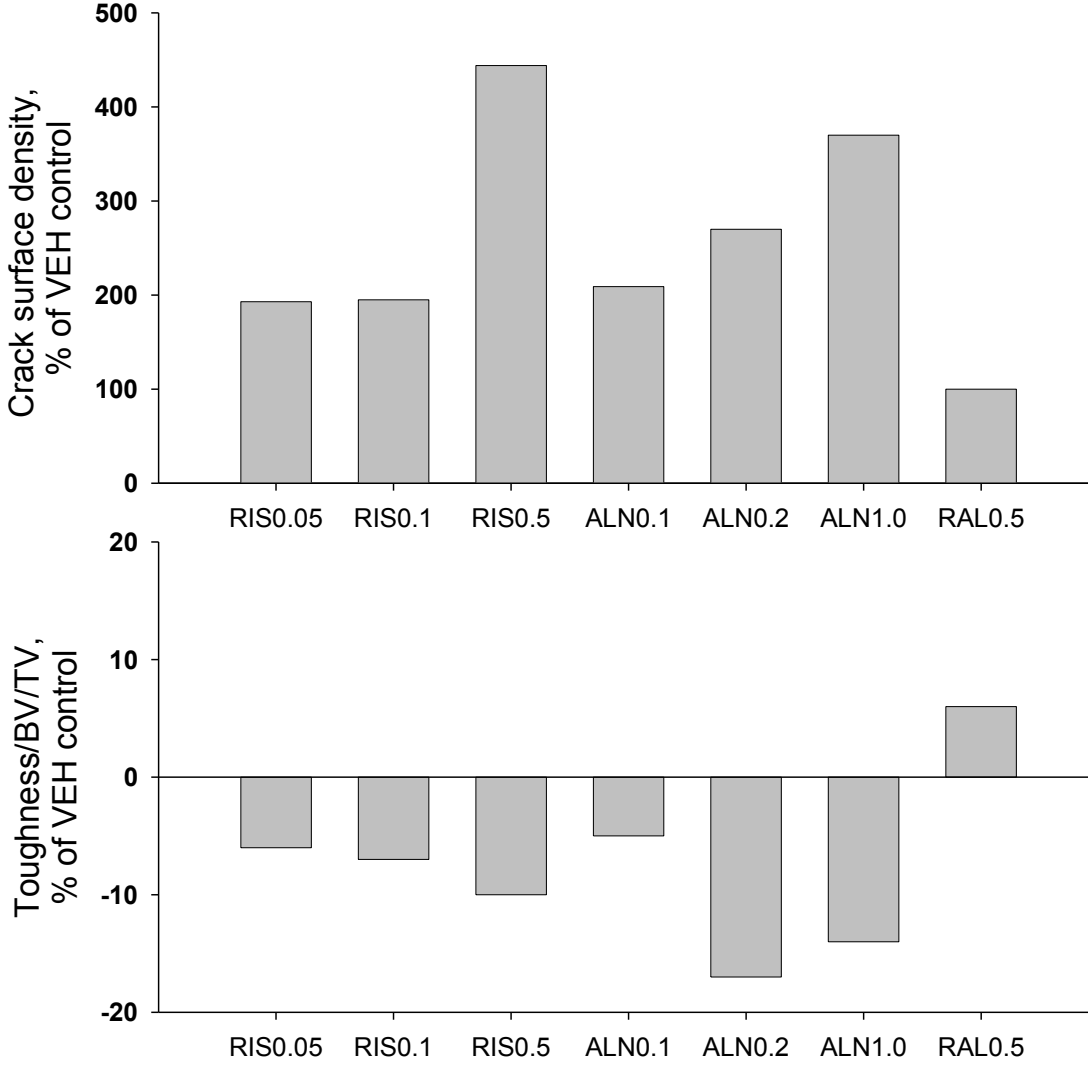
Fig 1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RAL0.5
Toughness/BV/TV,
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Fig 2

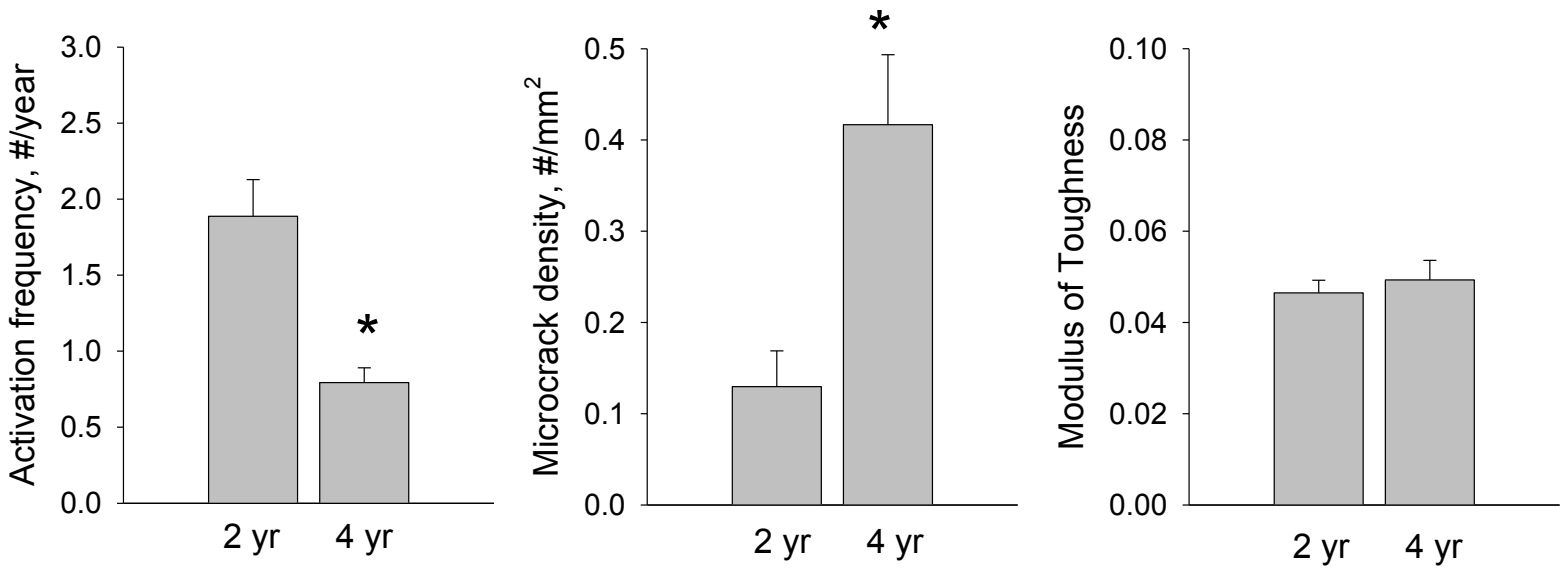
Activation frequency, #/year
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
2 yr
4 yr
Microcrack density, #/mm2
0.5
0.4
0.3
0.2
0.1
0.0
*
2 yr
4 yr
Modulus of Toughness
0.10
0.08
0.06
0.04
0.02
0.00
2 yr
4 yr

Fig 3

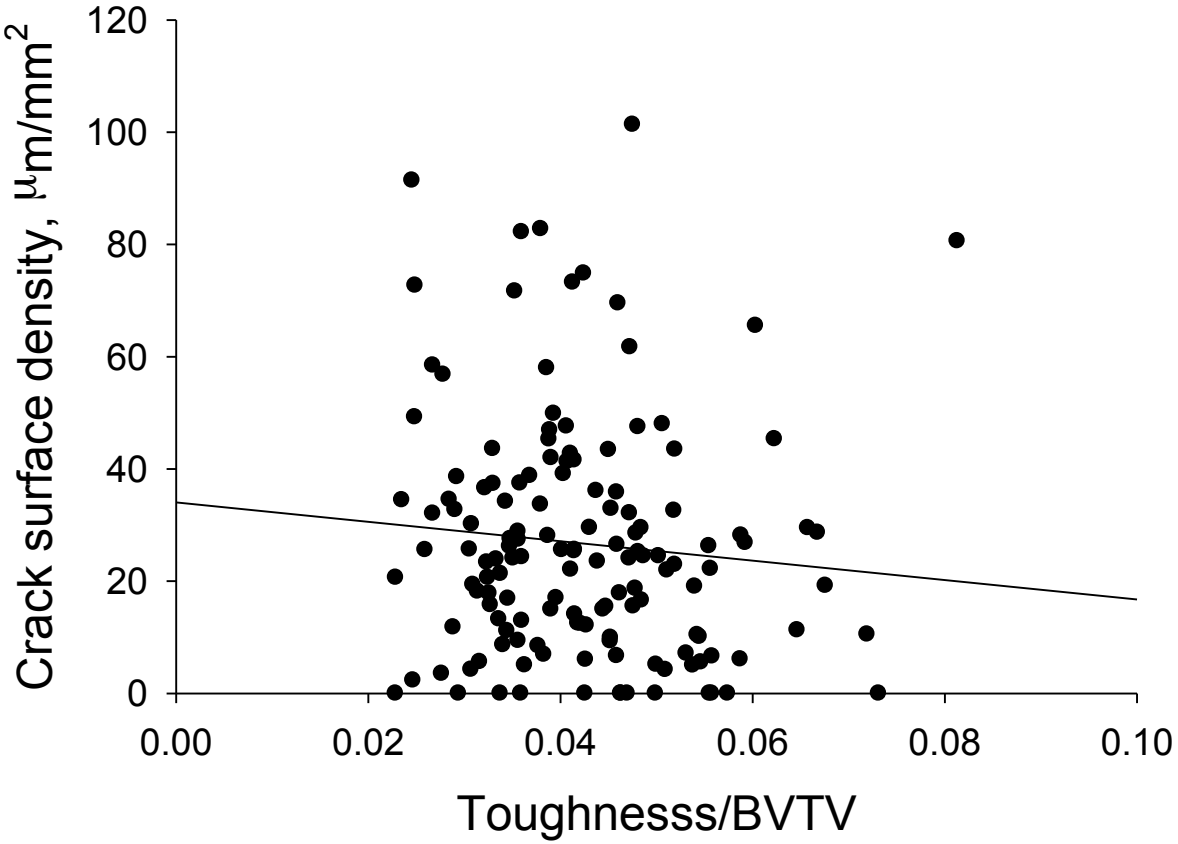
Crack surface density, μm/mm2
120
100
80
60
40
20
0
0.00
0.02
0.04
0.06
0.08
0.10
Toughnesss/BVTV

Fig 4

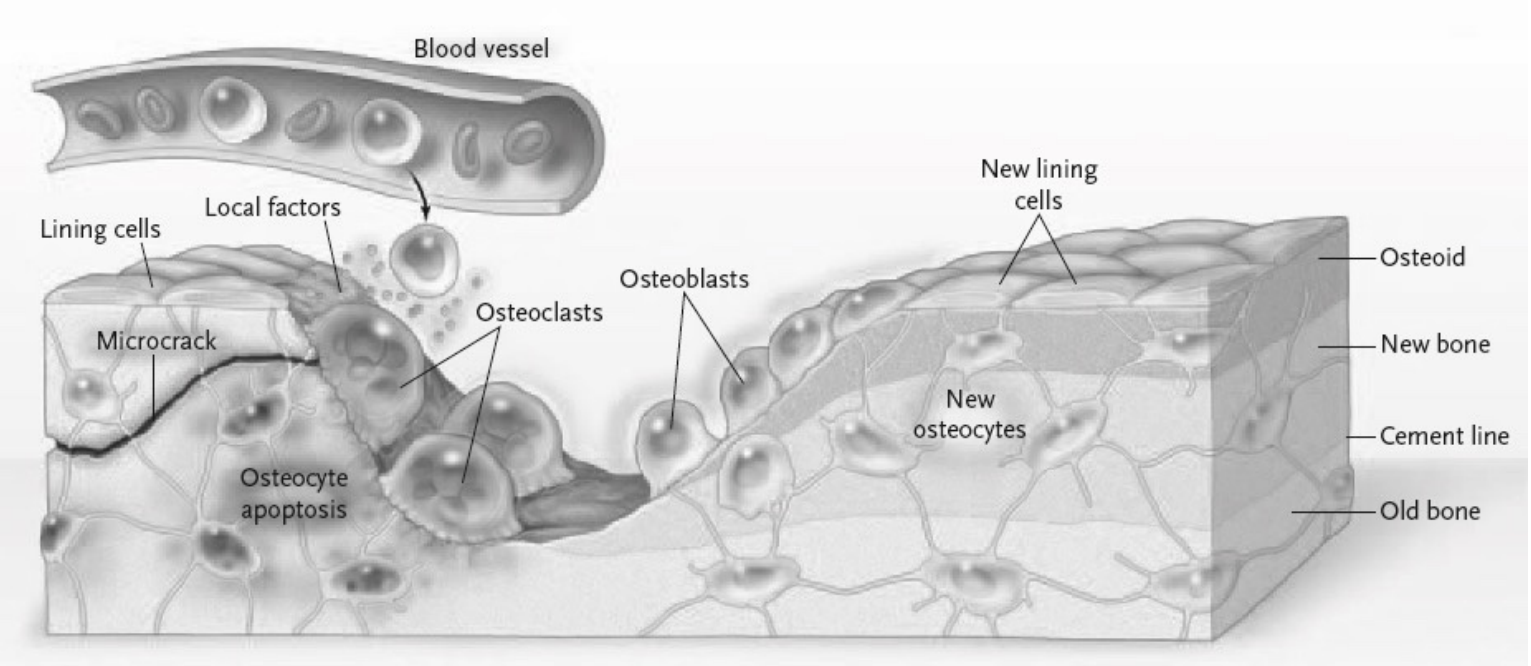
Blood vessel
Local factors
Lining cells
Microcrack
Osteoclasts
Osteoblasts
New lining cells
New osteocytes
Osteocyte apoptosis
Osteoid
New bone
Cement line
Old bone

Fig 5