J Musculoskel Neuron Interact 2002; 2(6):499-500

Perspective Article

Hylonome

Life history of osteocytes: relationship to bone age, bone remodeling, and bone fragility

A.M. Parfitt

Division of Endocrinology, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Keywords: Apoptosis, Lacunae, Iliac Biopsy

Osteocytes are the resident cells of bone, entombed while the bone is being made, connected to each other and to the lining cells on the surface by cell processes within canaliculi[1]. For the first few weeks the osteocyte is within osteoid and subsequently it is within mineralized bone. Each osteocyte undergoes one of two fates. Some die in situ by apoptosis; this process is brief, but apoptotic bodies can remain as a pyknotic nucleus for many months. Eventually the products of cell death are removed, leaving an empty lacuna. Much later (? years) the empty lacuna becomes filled with mineralized debris and may no longer be visible by light microscopy. Alternatively, some osteocytes may be removed before death by osteoclasts during bone resorption; their subsequent fate is controversial.

Most studies of osteocyte number have used the number of lacunae as the referent. Many years ago Frost found that percent occupied lacunae in human cortical bone fell from about 95% at age 10 to about 70% at age 40, and remained steady thereafter. The decline was greater in interstitial than in osteonal bone[2]. Much later osteocyte viability was determined using LDH cytochemistry, because osteocytes may remain stainable for some time after they have died. This index declined with age in the femoral head but not in the vertebral body[3]. Such results are of interest but assume that total lacunar density remains constant. Since this is not true it is more accurate to express such data as per unit bone area in a section, or better yet, although usually impractical, per unit bone volume.

My former laboratory at Henry Ford Hospital maintains a large library of iliac biopsy samples from healthy women. We found that cancellous osteocyte density (#/unit bone area) declined significantly with age from 20 to 70 years with a parallel decline in total lacunar density with an increase in empty lacunar density and a fall in the proportion of occupied lacunae[4]. The rates of change were most rapid initially, falling exponentially with increasing age. Linear regressions were all significant in premenopausal but not in postmenopausal women. When measurements were made separately in superficial bone (less than 25 μm from the surface) and in deep bone (more than 45 μm from the surface), at all ages there were significantly more osteocytes in superficial than in deep bone. There was no significant decline with age in superficial bone, but a steeper exponential decline in deep bone than in whole trabeculae. The results confirm that osteocyte density declines with age in women as it does in men[5] and suggest that it is the age of the bone rather than the age of the subject that is important, raising the possibility that one function of remodeling in iliac cancellous bone is to maintain osteocyte viability in superficial bone.

In iliac cancellous bone the probability that a particular episode of remodeling will penetrate to a region decreases with distance of the region from the surface[6]. Consequently, superficial bone is more frequently remodeled than deep (mainly interstitial) bone, so its mean age is lower, which is the primary difference between them. Even with a high rate of surface remodeling, bone more than 75 μm from the surface is virtually inaccessible and may be as old as its owner. Indeed, the remoteness of interstitial bone from remodeling and consequent protection against perforation is a condition for its survival. As well as fewer osteocytes, old interstitial bone has higher mineral density and more micro damage than young surface bone.

Since the density of empty lacunae in superficial bone does not fall with age, bone containing empty lacunae must be replaced by new bone containing osteocytes. We found a significant inverse relationship between superficial bone osteocyte density and surface bone formation rate (BFR) in healthy women, consistent with the suggestion that osteocytes released a signal that inhibits remodeling[7]. This raises the possibility of a feedback relationship between the two variables. However, a high BFR was unable to correct the osteocyte deficit and most of the variance in superficial bone

Corresponding author: A. Michael Parfitt, M.D., University of Arkansas for Medical Sciences, Division of Endocrinology, 4301 West Markham Street, Slot 587, Little Rock, AR 72205, USA
E-mail: parfittalwynm@exchange.uams.edu

Accepted 1 August 2002

osteocyte density is explained by total lacunar density, which reflects initial osteocyte density and has a high CV of about 20%. This suggests that surface remodeling maintains osteocyte density but does not regulate it, since new bone will have the same initial osteocyte density as had the bone that it replaces. The integrity of the lacunar canalicular network and the low density of superficial bone both contribute to calcium exchangeability, so that the inverse relationship between them may serve the interests of calcium homeostasis[8].

Osteocyte deficiency might contribute to bone fragility by promoting the accumulation of fatigue microdamage[1]. In patients with hip fracture mean percent osteocyte viability in the femoral head did not differ from age matched controls but the variance was greater and a subset of patients had abnormally low viability[3]. Paradoxically it has been reported that iliac osteocyte density is increased in patients with fragility fracture[5] but the control measurements were from autopsy samples, and deplasticised sections had been stored for about four years longer in the fracture subjects than in the controls[9,10] so that there may have been greater shrinkage of the sections. By contrast, in patients with unequivocal bone fragility manifested by spontaneous symptomatic vertebral fracture[11] we found 30% fewer osteocytes than in healthy women, a difference than was not the result of having less bone.

Very little is known about the mechanism of osteoblast incorporation into bone matrix as an osteocyte. Obviously to become an osteocyte an osteoblast must escape apoptosis, and possibly an increase in the proportion of osteoblasts dying might leave too few to become osteocytes. It has been suggested that when an osteoblast is committed to become an osteocyte it reduces its rate of matrix synthesis so that the adjacent osteoblasts travel further from the cement line, eventually burying the committed preosteocyte[12]. Conceivably, whatever signals are involved in the burial process could be defective and lead instead to osteocyte death, so that clarification of the mechanism of incorporation has become an important research priority.

Acknowledgments

In this talk I have been the spokesman for my current collaborators and former colleagues in the Bone and Mineral Research Laboratory of Henry Ford Hospital, Shijing Qiu, Saroj Palnitkar, and Dan Rao. My great thanks are due to them for permitting me to participate in their current research.

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