

# The role of osteocytes in bone regulation: Mineral homeostasis versus mechanoreception

D.M. Cullinane

Musculoskeletal Research Laboratory, Department of Orthopaedic Surgery, Boston University Medical Center, Boston, MA, USA

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## Abstract

Early work on the role of osteocytes in bone regulation suggested that the primary function of these cells was osteolysis. This lytic function was not precisely defined but included mineral homeostasis and at least the initiation of matrix remodeling, if not a primary role in remodeling. This paper is an attempt to promote the concept of osteocytic osteolysis as a method of systemic mineral homeostasis and to separate it from bone remodeling. Although recent investigations have pointed to mechanotransduction as a primary function of osteocytes, resulting in a general abandonment of the osteocytic osteolysis concept, the corpus of evidence suggests that osteocytes likely have a multipurpose role in the biology of bone. The osteocyte network represents an enormous surface area over which the cells interface with the surrounding matrix, useful for both strain detection and matrix mineral access. Osteocytes have been found to possess receptors for PTH, a known regulator of mineral ion homeostasis. Cultured osteocytes placed on dentin slices demonstrated no capacity to pit the dentin, but they were not treated with a regulating factor such as PTH, nor does mineral homeostasis require substantial bone volume removal. Scaling relationships suggest that osteocyte density is inversely proportional to body mass,  $R^2 = 0.86$ , and thus directly proportional to metabolic rate. Thus, species with higher metabolic rates (and therefore a greater demand for immediate access to minerals) have more osteocytes per bone volume. Finally, osteocytes express molecules typically associated with nerve cells and which are involved with glutamate neurotransmission. By this system, almost instantaneous messages may be transmitted throughout the network, an important feature in cells whose homeostatic function would be utilized on a scale of seconds, rather than hours or days. Experimental procedures for determining the role of the osteocyte in mineral homeostasis would require calcium mobilization from the bone matrix on a relatively immediate time scale. The experimental procedure would then be coupled with a high resolution histomorphometric analysis of lacunar radiographic area and mineral density. Added to this would be an *in vitro* study of mineral activation capacity via cultured osteocytes treated with PTH. Osteocytic osteolysis would be confirmed by an increase in the demineralized volume of osteocytic lacunae and the identification of a chemical mechanism by which osteocytes can readily access the mineral portion of their immediate bone matrix. It should also be true that a reverse capacity exists by which osteocytes can remineralize their immediate matrix utilizing alkaline phosphatase for example, a chemical which they, like osteoblasts, are known to generate. It is thus proposed that osteocytes are both mechanoreceptors and systemic mineral homeostasis regulators.

**Keywords:** Osteocytes, Mineral Homeostasis, Mechanoreception, Osteolysis

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Early work on the role of osteocytes in bone regulation suggested that the primary function of these cells was osteolysis<sup>1</sup>. This lytic function was not precisely defined but included mineral homeostasis and at least the initiation of matrix remodeling, if not a primary role in remodeling. The

evidence for osteolytic osteolysis was largely histological and microradiographical, with enlarged lacunae and reduced radiodensity in the bone of animals that had been mineral starved. Current concepts of osteocytic osteolysis suggest the lytic role of these cells is not bone matrix remodeling but systemic mineral homeostasis. Evidence against osteocytic remodeling of bone matrix has been misinterpreted as evidence against mineral mobilization and systemic mineral homeostasis. This paper is an attempt to promote the concept of osteocytic osteolysis as a method of systemic mineral homeostasis and to separate it from bone remodeling.

Corresponding author: Dennis M. Cullinane. Musculoskeletal Research Lab., Dept. of Orthopaedic Surgery, Boston University Medical Center, Boston, MA 02118, USA.

E-mail: bones@bu.edu

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Recent investigations have pointed to mechanotransduction as a primary function of osteocytes<sup>2</sup>, resulting in a general abandonment of the osteocytic osteolysis concept. The evidence for mechanotransduction comes principally from quantitative assays for gene upregulation including cAMP, osteocalcin and IGF-1 in response to mechanical load<sup>3</sup>. Osteocytes maintain an extensive and interconnected network via multiple processes within canaliculi and functional gap junctions<sup>4</sup>, ideal for a strain detection system or a mineral regulation network. The osteocyte network also represents an enormous surface area over which the cells interface with the surrounding matrix<sup>5</sup>, useful for both strain detection and matrix mineral access.

The corpus of evidence suggests that osteocytes likely have a multipurpose role in the biology of bone. Osteocytes have been found to possess receptors for PTH<sup>2</sup>, a known regulator of mineral ion homeostasis. Cultured osteocytes placed on dentin slices demonstrated no capacity to pit the dentin<sup>6</sup>, but the level of resolution of matrix depth in the study was only 2 microns which would not detect osteocytic osteolysis to a depth below a micron. The current osteocytic osteolysis concept does not suggest that osteocytes can, like osteoclasts, remove substantial quantities of whole bone matrix (organic and mineral phases). It suggests that they are capable of accessing bone matrix minerals to some relatively superficial depth, which multiplied by their immense surface area, would mean access to a substantial amount of mineral volume. In conjunction with this concept, osteocytes have in fact been shown to produce acid phosphatase, a known mobilizing agent of bone mineral<sup>7</sup>.

Further, scaling relationships suggest that osteocyte density is inversely proportional to body mass<sup>8</sup>,  $R^2 = 0.86$ , and thus directly proportional to metabolic rate<sup>9</sup>. Thus, species with higher metabolic rates (and therefore a greater demand for immediate access to minerals) have more osteocytes per bone volume (Fig. 1). Additionally, osteocytes express molecules typically associated with nerve cells and which are involved with glutamate neurotransmission<sup>2</sup>. By this system, almost instantaneous messages may be transmitted throughout the network, an important feature in cells whose homeostatic function would be utilized on a scale of seconds, rather than hours or days.

Experimental procedures for determining the role of the osteocyte in mineral homeostasis would require calcium mobilization from the bone matrix on a relatively immediate time scale. This could be effected by an *in vivo* model of calcium starvation and PTH treatment, for example. The instantaneous mineral demand and shortened experimental period would not allow for the confounding effect of osteoclast differentiation and activation. The experimental procedure would then be coupled with a high resolution histomorphometric analysis of lacunar radiographic area and mineral density, and TRAP staining. Added to this would be an *in vitro* study of mineral activation capacity. Cultured osteocytes could be treated with PTH and the surrounding media then assayed for mineral mobilizing

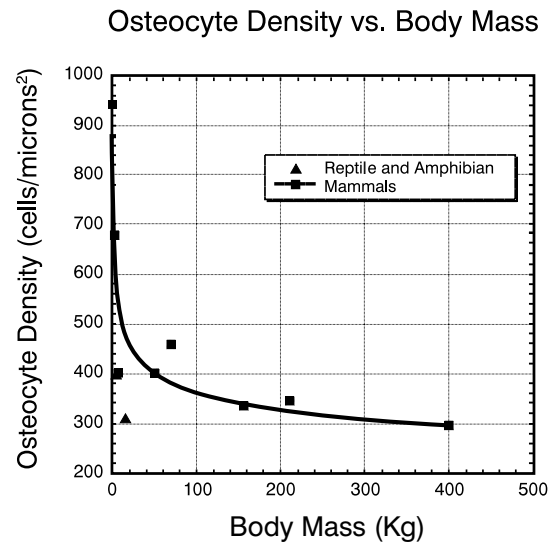


Figure 1. Osteocyte Density vs. Body Mass

molecules (TRAP). Osteocytic osteolysis would be confirmed by an increase in the demineralized volume of osteocytic lacunae and the identification of a chemical mechanism by which osteocytes can readily access the mineral portion of their immediate bone matrix. It should also be true that a reverse capacity exists by which osteocytes can remineralize their immediate matrix utilizing alkaline phosphatase for example, a chemical which, like osteoblasts, they are known to generate<sup>6</sup>.

In summary, osteocytes are ideal candidates for systemic mineral homeostasis regulation. They represent an enormous surface area, their density is proportional to a species' metabolic demands, radiographically they have demonstrated mineral matrix dissolution, and there is evidence that they have the biochemical capacity to both access and deposit matrix minerals. It is proposed that osteocytes are both mechanoreceptors and systemic mineral homeostasis regulators.

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