INTRODUCTION: Osteocytes appear to be the mechanical sensor cells in bone. The mechanism by which they perceive mechanical load is not known. One idea is that cell membrane stretch results directly from surrounding tissue deformation. If so, then strain on osteocyte membranes should be comparable to bone tissue strain. However, in vitro studies (1) show that inducing cellular response by direct mechanical deformation of bone cells requires deformations one to two orders of magnitude larger than bone strains normally experienced by the bone in vivo (0.3%). Similar cell strain magnitudes (~15%) are needed to activate fibroblasts and chondrocytes, suggesting that in their sensitivity to mechanical strain, osteocytes do not differ from other cells. However, in fibrous tissue and cartilage, large tissue-level strains, of the same magnitude as cell stimulating strains in vitro, are typically generated during physiological use. In bone, the high strains needed to stimulate osteocytes cannot be derived directly from matrix deformations, as they would cause bone fracture. Thus, in bone there is an inherent contradiction between material and biological stimulation requirements. We present here an hypothesis and model to deal with this contradiction.

METHODS: Osteocytes sit inside lacunae and are interconnected by cell processes running through canaliculi (Fig. 1). Between the osteocyte cell process membrane and canicular wall is the pericellular space, with its pericellular organic matrix that allows bone fluid to flow (Fig. 1). When a bone is deformed, the deformation-induced pressure gradient causes bone fluid to flow in the pericellular space of the lacunar-canicular system. This effect is exactly analogous to what happens when a sponge is squeezed. The pericellular matrix between the osteocyte and the canicular wall has potential attachments to both the cell membrane and the bony wall. Fluid flow in the pericellular space will induce a drag force on the pericellular matrix structure between the canicular wall and the cell process. Reaction to this drag force is provided by tension in the cell membrane and the drag on the fibers of the glycocalyx by the underlying intracellular actin cytoskeleton (IAC) can be deformed dramatically by this tensile stress (Fig. 1).

RESULTS: The ratio of drag force on the fibers induced by the flow to shear force on the process membrane is extraordinarily high in the physiological range of fiber spacing (5-20 nm), the spacing into which most matrix macromolecules falls. For example, at fiber spacing value of 7 nm (i.e., the spacing for proteoglycans which are thought to comprise the PCM) the drag force is at least 40 times larger than the shear force (Fig 2a). We also found that in the physiological range of applied loads, 1 to 20 MPa, or load induced bone tissue strains from 0.005 to 0.1 percent, the amplification ratio is huge. It varies from 79 to 866 and depends on loading frequency (Fig 2b).

DISCUSSION: Based on the simple concepts that mechanically-induced fluid flow will cause drag on the pericellular matrix around osteocytes and that pericellular matrix possesses attachments to the osteocyte and canicular wall, the current analyses show an extraordinary potential for amplification of the mechanical signal to osteocytes. Moreover, the current model provides a resolution to a fundamental paradox in bone physiology, namely, that the strains applied to whole bone (i.e., tissue level strains) are an order of magnitude smaller (0.04% to 0.3%) than the strains (1% to 10%) necessary to induce bone cell responses in vitro (4); we show that this is, indeed, possible to produce cellular level strains in bone that are more than 10-fold greater than tissue level strains. In addition, fluid flow-induced drag forces on the fibers that tether the cell to its surrounding extracellular matrix can be much greater that the fluid shear forces on the cell membrane, the fluid force that has been extensively studied until now. These results suggest that understanding the circumstances by which osteocyte experience their mechanical environment will require a comprehensive understanding of the manner in which they interact with their surrounding matrix. 

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