



## Angiotensin Converting Enzyme Inhibition: Therapeutic Implications in Fracture Healing

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Hypertension and osteoporosis are two major chronic diseases affecting the elderly. They are associated with disturbances in calcium metabolism, including increased urinary calcium, vitamin D insufficiency and decreased bone mineral density (1). Hence, there is an increased risk of fractures in this population. In recent times, tremendous research is being done on various modalities for augmenting fracture healing. Angiotensin Converting Enzyme (ACE) inhibitors have shown promise as an effective therapeutic option for this complex situation.

Tissue renin angiotensin aldosterone system (RAAS) exists in tissues that have the capacity for both the local generation and action of Angiotensin-II. Among the local RAAS, RAAS components can be found in the brain, heart, vasculature etc (2). Local RAAS has been implicated in inflammation, regeneration, apoptosis, cell growth and regeneration (3). It plays a deleterious role in actions of hypertension and diabetes. Different novel targets based on tissue RAAS are undergoing pre-clinical and clinical studies, and the postulated one are AT2 agonists, dual action antagonist of AT1 and endothelin ETA receptors, activation of ACE2- Ang-(1-7)-Mas receptors, (P) RR inhibitors and aldosterone syntheses inhibitors. However, role of local RAAS in bones is still in its premature stages and its role to still be explored.

In RAAS system, ACE leads to generation of Ang II as an effectors molecule. In various in vitro studies, it has been demonstrated that different components of the RAAS are expressed on the osteoblasts and osteoclasts.

(4,5,6). It influences the osteoblastic cell function through specific receptor binding via AT1 and AT2 receptors, where Ang II plays an important role in causing bone resorption, decrease in calcium uptake after stimulation with Angiotensin II and suppression of osteoblastic bone differentiation (6). Even during the normal growth RAAS components are expressed mainly as ACE in osteoblasts during endochondral bone formation in the growth plate (6).

Studies have shown that ACE inhibitor moexiprilat blunted the bone resorption and a recent study conducted by Garcia *et al.*, (7) reported that ACE is expressed in osteoblasts and hypertrophic chondrocytes in periosteal callus, during fracture healing. ACE inhibition with perindopril (Angiotensin converting enzyme inhibitor) improved periosteal callus formation, bone bridging of the fracture gap and torsional stiffness, thus improving bone healing and remodeling. The authors concluded that this positive effect was due to the inhibition of the apoptosis and increased expression of the AT 2 receptors. This is similar to the previous known fact that RAAS contributes to fibrogenesis in variety of organs like heart, vascular wall, pancreas, kidney and liver.

Similarly, Schurman *et al* (8) in their study showed that AT II decreases calcium uptake in the bone disc bioassay system. This effect can be abrogated by antibody to b-FGF or prostaglandin synthetase inhibition. These results support the hypothesis that in children with NBS, elevated levels of AT II stimulate local skeletal b-FGF

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synthesis, with a resultant increase in bone resorption via a prostaglandin-dependent pathway.

Lynn in his cross-sectional study of 3887 Chinese men (n = 1958) and women (n = 1929) showed the association between angiotensin converting enzyme inhibitor (ACEI) use and bone mineral density (BMD) by demonstrating that ACE inhibition caused improvement in bone health in elderly Chinese population. ACEI use was associated with higher femoral neck BMD (+0.015 g/cm<sup>2</sup>, P = 0.035) in women, and higher femoral neck (+0.015 g/cm<sup>2</sup>, P = 0.017), total hip (+0.016 g/cm<sup>2</sup>, P = 0.021), and lumbar spine (+0.043 g/cm<sup>2</sup>, P < 0.001) BMD in men (9).

In a similar study captopril, one of the most widely used ACEIs, has the potential effects of improving lumbar vertebral bone strength in aged OVX rats and promoting osteoblast bone formation in vitro (10).

The actual mechanism by which ACE inhibitors influence bone mass is not known but assumed that the therapeutic effect comes from decreased angiotensin II levels which acts on bone cells via a tissue-renin-angiotensin system that regulates blood flow in bone marrow capillaries and affects osteoclastic bone resorption which raises the possibility that bone has RAAS system (11) or by binding to AT1 receptors on osteoblasts thereby promoting the release of mediators that activate the osteoclasts (12) and also by influencing calcium metabolism by decreasing ionized calcium and increasing parathyroid hormone levels (13). Angiotensin II can interfere with calcium metabolism. The reduction of angiotensin II levels has a beneficial effect of inhibiting bone resorption and promoting mineralization.

Hence, ACE inhibition could be a possible novel therapeutic modality in those with fractures, so that it can accelerate the fracture healing process. Its positive effect on bone mineral density can be harnessed as an effective treatment modality in osteoporotic hypertensive individuals who are on the ACE inhibitors for the hypertension or associated cardiovascular system. Furthermore it will be very interesting to establish such relationship in an epidemiological studies in future.

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