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Inhibition on angiotensin-converting enzyme exerts beneficial effects on trabecular bone in orchidectomized mice

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ABSTRACT

Background: This study aimed to study the osteo-preservative effects of captopril, an inhibitor on angiotensin-converting enzyme (ACE), on bone mass, micro-architecture and histomorphology as well as the modulation of captopril on skeletal renin-angiotensin system (RAS) and regulators for bone metabolism in mice with bilateral orchidectomy.
Methods: The orchidectomized (ORX) mice were orally administered with vehicle or captopril at low dose (10 mg/kg) and high dose (50 mg/kg) for six weeks. The distal femoral end, the proximal tibial head and the lumbar vertebra (LV) were stained by hematoxylin and eosin, Safranin O/Fast Green and masson-trichrome. Micro-computed tomography was performed to measure bone mineral density (BMD).
Results: Treatment with captopril increased trabecular bone area at distal metaphysis of femur, proximal metaphysis of tibia and LV-4, moreover, high dose of captopril significantly elevated trabecular BMD of LV-2 and LV-5. The mRNA expressions of renin receptor, angiotensinogen, carbonic anhydrase II, matrix metalloproteinase-9, and tumor necrosis factor-alpha were significantly decreased in tibia of ORX mice following treatment with captopril. The administration with captopril enhanced the ratio of OPG/RANKL mRNA expression, the mRNA expression of transforming growth factor-beta and the protein expression of bradykinin receptor-1.
Conclusions: The inhibition on ACE by captopril exerts beneficial effects on trabecular bone of ORX mice. The therapeutic efficacy may be attributed to the regulation of captopril on local RAS and cytokines in bone.

Introduction

Osteoporosis is a disease that thins and weakens bones to the point that they become fragile and easily break. It is well-known that osteoporosis-related fractures due to low-trauma or fragility result in heavy health-related costs, substantial disability and mortality among postmenopausal women and older men [1]. Osteoporosis is now recognized as a major threat to health in aging people. Men sustain bone loss of approximately 0.5–1% per year from the sixth decade despite not undergoing a menopausal transition as women do [2]. Overall, the trend of age-adjusted prevalence of osteoporosis was similar between women and men [3,4]. However, the mortality and morbidity caused by osteoporotic fractures are greater in men with testosterone deficiency-induced osteoporosis than those in women with postmenopausal osteoporosis [5,6].

Bone metabolism is normally modulated by regulators and cytokines in bone micro-environment. The expression ratio of osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANKL), both of which are secreted by osteoblasts, determines the maturation of osteoclasts. Matrix metalloproteinase (MMP)-9 and carbonic anhydrase (CA)II produced from osteoclasts are responsible for resorbing organic proteins and inorganic minerals, respectively. Bradykinin manages bone metabolism through modulating osteogenesis and osteoclastogenesis by binding to its receptor. Recently, various cytokines like tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β are found to play major roles in bone health.

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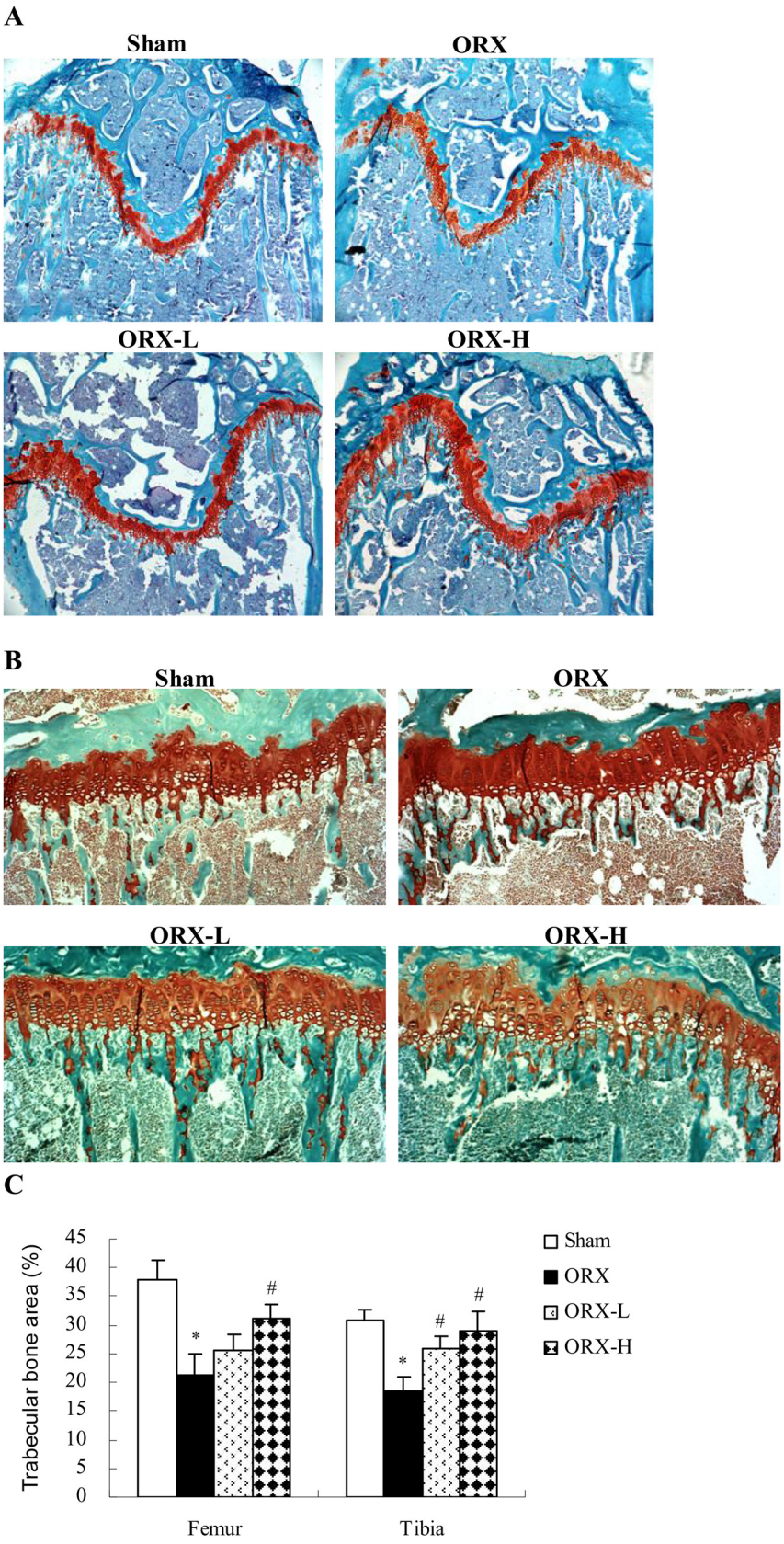

Fig. 1. Histological image measured by Safranin O/Fast Green staining. Femurs and tibias were collected from Sham mice and ORX mice orally treated with vehicle (ORX), or captopril with low dose (ORX-L, 10 mg/kg) or high dose (ORX-H, 50 mg/kg) for 6 weeks. A, distal femoral end (magnification, ×50). B, proximal tibial head (magnification, ×100). C, trabecular bone area under growth plate in femur and tibia was quantified. Values were expressed as means ± SEM, n = 8; * $p < 0.05$ *vs.* Sham group, # $p < 0.05$ *vs.* ORX group.