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Effects of raloxifene against letrozole-induced bone loss in chemically-induced model of menopause in mice

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Introduction: The deleterious effects of letrozole, an aromatase inhibitor, used in the adjuvant treatment of breast cancer in postmenopausal women, on bone are well-documented and represent a major drawback to its clinical use. Raloxifene, a selective estrogen receptor modulator and a clinically approved anti-osteoporotic drug, has been recently demonstrated to be efficacious in women with breast cancer. The present study evaluated the effects of preventive and curative treatment with raloxifene on letrozole-induced alterations of bone microarchitecture and turnover markers in a chemically-induced menopause model in mice.

Method: Swiss strain albino female mice were made menopausal by inducing ovotoxicity using vinyl cyclohexene di epoxide (VCD, 160mg/kg for 15 days followed by 30 days drug-free period) confirmed by ovarian histology and serum estradiol levels. Effects on femoral and lumbar bones were evaluated by micro CT determination of bone volume, trabecular number, separation, thickness, connective density and trabecular pattern factor and bone turnover markers including ALP, TRAP5b, hydroxyproline and RANKL. In addition to these, markers of Wnt signaling (sclerostin and dickkopf-1) were also evaluated. To rule out the involvement of pharmacokinetic interaction, plasma levels of letrozole and raloxifene were measured following drugs alone and in combination.

Results: Though bone loss was observed in VCD treated mice (as indicated by micro CT measurements), it was further enhanced with letrozole administration (1 mg/kg) for one month particularly in epiphysis of femoral bones but also in lumbar vertebrae. Raloxifene (15 mg/kg), whether administered concurrently or post-letrozole was able to revert the structural alterations and changes in turnover markers caused by letrozole to varying degrees ($p<0.01$ or $p<0.001$). Further, estrogen deficiency following letrozole treatment in ovotoxic mice was associated with significant increase in sclerostin and dickkopf-1 in both lumbar and femur bones ($p<0.001$) which was attenuated with preventive and curative treatment with raloxifene ($p<0.05$). Further, plasma levels of letrozole remained unaffected by raloxifene administration and vice versa.

Conclusions: Our study, thus, holds promise for raloxifene in preventing and attenuating letrozole-induced bone loss as indicated by structural changes and alterations in bone turnover markers and suggests that it not only controls osteoclastogenesis via RANKL axis but also has the potential to affect osteoblastogenesis via recently emerged Wnt pathway. Further, these effects were found to be independent of a pharmacokinetic interaction between the two drugs.