Hyperhomocysteinemia: Can't it account for retinoid-induced fracture proneness?

Sir,

A substantial amount of animal studies[1-3] and some human studies have shown that retinoid use is associated with osteoporosis and an increased risk for bone fracture.[4,5] The mechanism of this effect has been elusive. In 1986, McGuire and Lawson.[5] suggested a possible relationship of the retinoid use with elevation of some cytokines that can enhance maturation of the preosteoclasts.[5] Later on, histomorphometric evaluations revealed that activation of osteoclasts and increased subperiosteal osteoclastic bone resorption

may be the mechanism of bone loss due to retinoids.[2,3] Administration of retinol with alendronate sodium, a direct potent inhibitor of osteoclasts action,[3] lessened the preventive action of alendronate on the development of osteopenic changes in the skeletal system of ovariectomized rats.[6]

We herein suggest a hitherto unexplained mechanism for retinoid osteoporotic adverse effect and increasing risk of bone fractures that could lead to novel preventive strategies.

The aminoacid homocysteine (Hcy) is metabolized in the liver by cystathionine beta-synthase.[7] Hcy levels are shown to be elevated in patients on isotretinoin treatment for acne, which may be due to the inhibition of cystathionine beta-synthase by the drug and/or the drug-induced liver dysfunction.[7,8] Elevated levels of Hcy have been linked to increased fracture in the elderly and have been suggested as a new risk factor for osteoporosis.[9,10] Epidemiological and randomized clinical trials suggest that hyperhomocysteinemia increases fracture risk, but has minor effects on bone mineral density. Hcy has been found to accumulate in the bone by collagen binding and stimulate osteoclasts but not osteoblasts, thereby inducing a shift of bone metabolism toward resorption. In addition, hyperhomocysteinemia seems to have adverse effects on extracellular bone matrix by disturbing collagen crosslinking.[9]

So, putting these facts altogether, it could be suggested that retinoid-induced hyperhomocysteinemia may account for osteoclast overactivity, osteoporosis, and increased risk of bone fracture associated with retinoid use. Daily supplementation with vitamin B_{12} and folate, which are the cofactors of the enzymatic reactions involved in Hcy metabolism, can lower plasma levels of Hcy[7] and prevent osteoporosis[11] induced by retinoid and other potential untoward effects of hyperhomocysteinemia such as atherosclerosis.

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DOI: 10.4103/0378-6323.60557 -

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