Homocysteinemia and Bones

9

9.1 Homocysteinemia and Bones

As per Fig. 1.1, metabolism of homocysteine can be through oxidation to homocysteic acid by the action of vitamin C. This homocysteic acid is required for the synthesis of sulphated proteoglycans which are an integral part of the connective tissue in the walls of the blood vessels as well as in the bones.

Liu et al. (1997) showed that homocysteine thiolactone inhibited lysyl oxidase (by decreasing the expression of the LOX gene) and, thereby, interferes with the post-translational modification of collagen. Homocysteine selectively promotes chondroitin sulphate so that the chondroitin/dermatan sulphate ratio is maintained when homocysteine is within the biological reference interval; this homeostasis is altered in the presence of homocysteinemia (Fujiwara et al. 2008). Both these processes result in an altered collagen fibre with decreased strength.

Also, homocysteinemia is known to increase osteoclast activity, decrease osteoblast activity and activate matrix metalloproteinases (MMPs). MMPs are activated in the mitochondria by hypochlorous acid (HOCl) which is generated from hydrogen peroxide (H_2O_2) by the action of myeloperoxidase, an enzyme that is induced by homocysteinemia and oxidative stress (Fu et al. 2001). This is the pathway for activation of MMP-7. MMP-9 activation is affected through mitochondria via another pathway. Homocysteine activates and translocates calpain-1 from the cytosol to the mitochondria, increasing the intramitochondrial stress and activating MMP-9 (Moshal et al. 2006). These MMPs then degrade the extracellular bone matrix. In addition, there is a reduced blood flow to the bones due to vascular remodelling subsequent to homocysteinemia. The result is remodelling of bone matrix and increased susceptibility to fractures (Hermann et al. 2005).

In addition to remodelling of bones, it has also been demonstrated that the MMPs play an important role in healing and repair of fractures; MMP-7 and MMP-12 have been found in non-healing fractures, confirming this finding (Fajardo et al. 2010). Conversely, MMP inhibitors have been shown to aid bone resorption by causing

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cleavage of the triple helices of collagen 1, resulting in its degradation (Murphy and Reynolds 1985).

Bosch-Marcé et al. (2005) suggested that increased vascular resistance due to impaired angiogenesis, as a result of homocysteinemia, could result in decreased blood flow. Tyagi et al. (2011) demonstrated a decreased blood flow in the tibia secondary to homocysteinemia in a homocysteinemic mouse model.

Blouin et al. (2009) obtained a correlation between homocysteine and bone marrow density ($p < 0.05$), indicating that homocysteinemia may not directly alter the density but affects the quality of the bone matrix by altering the collagen cross-links. Morris et al. (2005), however, demonstrated that subjects with homocysteine ≥20 μmol/L had a lower BMD (bone marrow density) than those with homocysteine <20 μmol/L, making them more prone to fractures and osteoporosis.

In addition to increase in MMPs, bone matrix can be affected directly by the homocysteine molecule or thiol binding to the collagen which is mostly type I. Herrmann et al. (2009) demonstrated that 65% of the total homocysteine binds to collagen type I in the extracellular matrix of the bone.

Thus, it is evident that homocysteinemia would impair bone matrix, increasing the probability of fractures and also would impede the healing process.

Lacunae in Knowledge

There are limited human case-control studies elucidating the relationship between altered bone metabolism in the presence of homocysteinemia and the benefits of the B vitamins/metabolic modulators.

Clinical Message

In the presence of homocysteinemia, care must be taken to reduce homocysteine by appropriate vitamin supplements. Care must also be taken to prevent fractures.

When a fracture has occurred, blood levels of homocysteine and its determining vitamins must be estimated and appropriate measures taken in the presence of homocysteinemia or deficiency of folate or B_{12}.