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Iron loading: a risk factor for osteoporosis

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Abstract

Iron loaded persons are at increased risk for infection, neoplasia, arthropathy, cardiomyopathy and an array of endocrine and neurodegenerative diseases. This report summarizes evidence of increased risk of iron loading for osteoporosis. Iron suppresses bone remodeling apparently by decreasing osteoblast formation and new bone synthesis. Low molecular mass iron chelators as well as a natural protein iron chelator, lactoferrin, may be useful in prevention of osteoporosis.

Introduction

Excessive and misplaced iron presently is recognized as a risk factor for infection, neoplasia, arthropathy, cardiomyopathy, and an array of endocrine and neurodegenerative diseases (Weinberg 2006). Moreover within recent years, in patients with iron loading conditions, reports increasingly have been published of osteopenia and osteoporosis.

Association of iron loading disorders with osteoporosis

That iron is directly toxic to bone remodeling has been observed in several studies (Table 1). For instance, iron overload in pigs, at the same magnitude as in untreated hemochromatotic persons, markedly decreased osteoblast formation and new bone synthesis whereas osteoclast resorption surfaces were unchanged (de Vernejoul *et al.* 1984). Serum levels of vitamin D and parathyroid hormone remained normal.

In a set of 38 untreated, HFE-related hemochromatotic patients, 79% were osteopenic and 34% osteoporotic (Guggenbuhl *et al.* 2005). Vitamin D serum levels were normal, no parathyroid dysfunction was found, and only 13% were hypogonadal.

Low bone mass was present in 61% of 18 transfused thalassemic children (age 5.8 ± 1.5 year) despite optimal chelation, adequate growth and lack of endocrine complications (Vogiatzi *et al.* 2004). In a group of 41 thalassemic patients with regular transfusions, 17 (8 with and 9 without desferrioxamine chelation) had osteoporosis (Chan *et al.* 2002).

In a set of 17 consecutive sickle cell anemia adult patients with blood transfusion history, 47% had osteopenia. Hepatic iron and serum ferritin levels were significantly greater in osteopenic than in non-osteopenic patients (Shah *et al.* 2004). Iron chelation therapy as well as hypogonadism were excluded as possible contributory factors.

Osteoporosis accompanying iron overload has been observed also in patients with African siderosis. In a study of femoral neck fractures in 50 black patients, 88% were iron loaded (Schnitzler *et al.* 2005). The authors noted that iron overload accounted for a reduction in the rate of mineral

Table 1. Iron loading conditions associated with osteoporosis.

Condition	Number of Subjects	Observation	Reference
I. V. iron in pigs	5	Decreased number and activity of osteoblasts	deVernejoul *et al.* 1984
Hemochromatosis:			
Juvenile	1	Increased bone resorption	Angelopoulos *et al.* 2006
CY/CY	3	Femoral head aseptic osteonecrosis	Rollot *et al.* 2005
CY/CY	38	79% osteopenic; 34% osteoporotic	Guggenbuhl *et al.* 2005
Thalassemia:			
Children	18	60% low bone mass	Vogiatzi *et al.* 2004
Adults	41	41% osteoporotic	Chan *et al.* 2002
Sicklemia adults	17	47% osteoporotic	Shah *et al.* 2004
African siderosis	44	Reduction in mineral apposition rate	Schnitzler *et al.* 2005
HIV infection	161	49.7% osteopenic/ osteoporotic	Fausto *et al.* 2006

apposition whereas ascorbic acid deficiency was associated with decrease in bone volume.

During HIV infection, particularly in its more advanced stages, iron has been repeatedly observed to accumulate in such sites as bone marrow, brain, muscle, liver and spleen (Weinberg *et al.* 2002). Apparently, bone itself also may be a receptacle for the metal. In a group of 161 patients, 80 had osteopenia/osteoporosis (Fausto *et al.* 2006). The condition was associated with increased HIV-RNA levels but not with anti-retroviral therapy.

Prevention of iron-induced osteoporosis

Predictably, lifestyle behavior that prevents iron loading should be associated with good bone mineral density (BMD). Thus postmenopausal women with a habit of tea drinking have higher BMD than that of non-tea drinkers (Chen *et al.* 2005). A green tea iron chelator, (-)-epigallocatechin-3-gallate, has been observed to stimulate mineralization of murine bone marrow mesenchymal cell cultures (Chen *et al.* 2005).

A natural iron scavenging protein, lactoferrin (Lf), likewise might be predicted to maintain iron balance in the bone remodeling process. In a study of human CD14 selected cells committed toward osteoclasts, physiological concentrations of bovine apoLf ($\sim$ 15% iron saturated) inhibited bone resorbing activity (Lorget *et al.* 2002). Similarly, in murine bone marrow cultures, osteoclastogenesis was suppressed by bovine apoLf (Cornish *et al.* 2004). Moreover, in cultures of rat or human osteoblast-like cells, bovine apoLf substantially reduced apoptosis and markedly increased osteoblast proliferation. Oddly, similar results were stated to occur with human recombinant holoLf. It would be of considerable interest to test bovine holoLf as well as human apoLf in these culture systems. In any case, the authors have observed that Lf is anabolic to bone *in vivo* and have suggested that the protein might be useful as a local agent to promote bone repair.

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