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Editorial

Osteoporosis in Survivors of Childhood Malignancy

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THE DETECTION of late sequelae in survivors of childhood malignancy has become increasingly important as long-term survival is achieved and clinics set up for this purpose have identified novel sequelae. It is from such clinics that the first reports emerged of fractures in osteoporotic individuals who had survived malignant brain tumours or acute lymphoblastic leukaemia (ALL) [1, 2]. However, the prevalence of osteopenia is only beginning to be appreciated and the reasons for its genesis are largely unknown.

Peak bone mass is reached during the second or third decade, after linear growth is complete, following the rapid accumulation of skeletal mass that occurs during adolescence and early adulthood [3]. This is achieved under the influence of growth hormone (GH) mediated by insulin-like growth factor-1 (IGF-1), with a clear association between linear growth and build up of bone mass [4, 5]. At puberty, there is synergism between increased secretion of GH/IGF-1 and the presence of sex steroids leading to the growth spurt [6] and GH may have a role in the additional increase in bone mass after completion of linear growth [5]. Both cortical and trabecular bone contribute to the mechanical strength of the skeleton and the relative proportion of each depends on the site studied. The spine, for example, has a high proportion of trabecular bone which is more responsive to metabolic stimuli than cortical bone. The magnitude of the peak bone mass is one of the most critical factors in determination of involutional osteoporotic fracture risk [3].

In ALL, osteopenia and other skeletal abnormalities have long been associated with the disease process as they are present at diagnosis. Radiological features include lytic and sclerotic lesions, metaphyseal lucencies, periosteal elevations, osteopenia, osteoporosis and fractures [7]. At diagnosis osteopenia may be associated with consistently low levels of both 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2$ D_3), the active metabolite of vitamin D and osteocalcin, synthesised under its influence by osteoblasts. These changes suggest defective bone formation and although hypercalciuria may occur, markers of bone resorption appear normal [8].

Therapy-related skeletal morbidity, characterised by osteopenia and fractures, is also recognised. In a longitudinal study conducted by Halton and colleagues (1996), mineral metabolism and bone mass was assessed in 40 children during treatment for ALL over 2 years [9]. A high incidence of bone pain, abnormal gait and unusual fractures was found in both standard- and high-risk patients, all in remission and receiving maintenance therapy. The incidence of radiographic changes, compatible with osteopenia, rose from 10% at diagnosis, to 76% at 24 months of treatment, although the reduction in bone mineral density (BMD) and bone mineral content (BMC) Z scores, by dual energy X-ray adsorptiometry (DEXA), was not significantly different from controls. Patients in this study received more frequent pulses of steroids (3-weekly) at a greater dosage (120 mg/m^2 daily in those at high-risk) than generally would have been given in U.K. protocols, which might account for the apparently high incidence of morbidity in this study.

Biochemical markers of bone formation and resorption and mineral status were also studied [9]. It was confirmed that circulating osteocalcin, active in bone formation, was low at diagnosis but normalised by 6 months on therapy, suggesting that bone mineralisation occurs during treatment. However, urinary excretion of type 1 collagen cross-linked N-telopeptide, a sensitive marker for bone resorption, was elevated throughout treatment. This, coupled with a progressive reduction in bone mass, suggests that increased bone resorption may occur as a consequence of treatment. The low concentrations of 1,25-$(OH)_2$ D_3 found at diagnosis persisted throughout treatment. Hypomagnesaemia also occurred in 84% by 6 months of therapy and hypercalciuria in some [9].

The most obvious culprits in the pathogenesis of therapy-related skeletal morbidity are the corticosteroids. Bone mineral loss due to both increased bone resorption and reduced bone formation is mediated through interference with calcium absorption from the gut. In addition, increased urinary excretion of calcium, disordered 1,25-$(OH)_2$ D_3 synthesis and secondary hyperparathyroidism have been reported [10, 11], all of which may occur during leukaemia treatment [9]. Methotrexate, too, has been implicated in the bony changes found in ALL and in infants treated for brain tumours with high-doses of this drug [12, 13]. High cellular levels of polyglutamates resulting from folate deficiency or inhibition of osteoblast proliferation are likely explanations for such toxicity [13, 14].

We know that radiographic and early therapy-related biochemical changes tend to improve once treatment is stopped

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[15, 16], although 1,25-$(OH)_2$ D_3 may remain undetectable in some patients at least 6 months after cessation of chemotherapy [16]. The reduced bone mineralisation found during therapy may remain unchanged in the immediate post chemotherapy period [16], but may be totally reversible one year after completion of treatment [17]. Other authors report bone mineralisation defects many years later in adult long term survivors of childhood ALL [1, 2, 18–20]. In one study, using DEXA at lumbar spine, femoral neck, trochanter and radius, a mean of 14.1 years from the end of treatment, at least 20% had one or more BMD Z score values greater than 2 SD below the mean of age- and sex-matched reference data controls [19]. Others have reported late osteopenia but found the trend towards normalisation of BMC over a period of years [18]. This leads one to speculate that there may be more than one aetiology in the pathogenesis of osteopenia and their summation may ultimately lead to reduced bone mass. Whilst disease, chemotherapy and steroids are strong contenders for the early pathogenesis, a different mechanism may come into play as time passes. Gilzanz and colleagues (1990) reported vertebral trabecular bone density, measured by quantitative computed-tomography, to be 10% lower in ALL survivors than in age-, sex- and race-matched non-leukaemic controls, 6–98 months (mean 42) after cessation of chemotherapy. This decrease was accounted for solely by those patients who had received cranial irradiation. Corticosteroids and chemotherapy administration was common to both irradiated and non-irradiated subjects [2].

Growth hormone deficiency and growth failure induced by cranial irradiation is a frequent complication of treatment for ALL and brain tumours [21]. Growth hormone deficiency has been widely reported to give rise to bone mineralisation defects [5, 24] and recombinant GH therapy can benefit bone density, quality of life, body composition and exercise capacity in hypopituitary adults and those with isolated GH deficiency [22, 23]. It has been suggested, in a large study ($n = 64$) of long-term survivors of ALL and brain tumours, that bone mineralisation and adult bone mass are protected by giving GH replacement therapy to GH-deficient individuals during childhood and adolescence [1]. Although these individuals may have received inadequate growth hormone replacement (GH being administered thrice weekly rather than daily) in terms of skeletal growth (they were shorter than non-GH deficient controls), none the less their bone mineral density was preserved. Similar GH-deficient patients untreated with GH were osteopenic. This suggests that even small-doses of GH may be protective for bone mass [1, 24]. However, Kaufman (1992) found that early GH substitution did not prevent defective bone mineralisation. None the less, cessation of GH did not result in bone loss [5]. Therefore, it begs the question as to whether GH therapy should be continued after skeletal growth is complete knowing that peak bone mass is not achieved until around the second to third decade.

In the current issue of this journal, Barr and colleagues (pp. 873–877) have attempted to shed further light on the role of cranial irradiation in the pathogenesis of osteopenia in survivors of childhood malignancy. They undertook a cross-sectional study of 19 long-term survivors of brain tumours on average 7 years after the end of treatment. These patients received much higher doses of cranial irradiation than patients with ALL and were, therefore, more likely to suffer GH deficiency. 6 patients were judged to be GH-deficient with growth velocities less than the third centile and confirmed on pharmacological testing. 5 of these received treatment with GH for a minimum of 3 years. The other 13 were deemed not to be GH-deficient solely because they had normal growth velocities. Osteopenia was assessed, by a single observer, from plain antero-posterior radiographs at various sites and by measurement of BMD at lumbar spine and femoral neck by DEXA. BMD was compared with normative standards provided by the manufacturer. Questionnaires detailing health-related quality of life and physical activity were also undertaken.

Radiographic assessment showed 9 patients to be osteopenic, including all 6 with GH deficiency and 10 not osteopenic, but the majority had negative BMD Z scores on vertebral bone densitometry (mean -0.98) and at the femoral neck (mean -0.64). For those who were osteopenic on plain X-ray, the mean BMD Z score at lumbar spine was significantly lower (-1.47) than in those who were not radiographically demineralised (-0.53), although there was no difference between groups at the femoral neck. The 6 GH-deficient children all of whom were osteopenic on X-ray showed lower mean BMD Z scores (-1.13 at lumbar spine and -1.45 at femoral neck) despite treatment with growth hormone in 5. These scores were not significantly different from those of the 13 non-GH-deficient patients (-0.45 at lumbar spine and -0.76) at femoral neck). This led to the conclusion that factors other than GH deficiency were primarily responsible for this particular late effect and that the aetiology was likely to be multifactorial.

Although contributing to our growing base of knowledge, I have reservations about the ability of this study to provide the answer to the questions set by the authors. The patients all received high radiation doses but only the third growing poorly were formally tested for growth hormone deficiency by pharmacological provocation, making a diagnosis of normal growth hormone status in the others only tentative. Unquantified radiographic assessment of osteopenia by plain X-ray also has limitations and may only be useful when severe bone loss has occurred (BMD values $< 0.73\,g/cm^2$). It has been reported that there is substantial inter-observer variation in evaluation of osteopenia by this method at higher BMD values [2, 25]. Bone densitometry generally is more accurate, providing the proportional relationship between bone size and, thus, height and bone mineral content are recognised and controlled [26]. Finally, the lack of difference in BMD scores between the GH deficient patients receiving replacement therapy and those considered not to be GH-deficient may simply reflect that GH did, indeed, have a protective effect on the bones, abolishing any differences between the two groups, whilst not preventing osteopenia totally.

I find myself in agreement with the authors that osteopenia is a common form of early and late morbidity in children receiving active cancer therapy and in those who have completed their treatment. There is little doubt that the evolution of the early changes is compatible with disease onset and steroid and chemotherapy administration. Given reports of resolution of these changes with cessation of cancer therapy it is conceivable that there may be 'a window' before the onset of late changes, in which variable degrees of resolution occur. At this stage other factors such as nutrition, exercise, smoking, genetic and endocrine factors and disease relapse also may influence the process of bone turnover [3].

GH deficiency undoubtedly occurs in many irradiated patients. Its onset may be delayed, the speed and degree of insufficiency depending on the radiation dose and fractionation schedule and age of the patient [21]. There is little dispute that GH deficiency can give rise to osteopenia in hypopituitary patients and there is considerable evidence that this may be a factor in the late skeletal morbidity of cancer therapy [1, 20]. It is attractive to think that osteopenia might be prevented by GH therapy in selected patients and that such treatment, if continued until peak bone mass is achieved, might further reduce morbidity and fracture risk in adulthood. As discussed, there is some evidence to suggest a protective effect of GH but the story is not a simple one and we do not yet have all the answers. Added to this is the difficulty of obtaining GH for young adult patients in the current climate of rationing.

The treatment of established osteoporosis with restoration of the structural integrity of the skeleton is a challenge yet to be successfully fought and the importance of early prevention cannot be over emphasised. It is to this end that all involved in the treatment of cancer should strive, and the quest for better understanding of the pathogenesis of osteopenia advanced.

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