Leading article

Bone disease after liver transplantation

It is well known that bone problems occur in patients with chronic liver disease, both cholestatic and non-cholestatic.[1-3] Bone disorders associated with chronic liver disease may be classified on a histological basis into osteomalacia, a reduction in mineralisation of bone matrix and osteoporosis, a reduction in total bone mass but with normal mineralisation. Osteomalacia in patients with liver disease occurs particularly with cholestatic disease, is associated with vitamin D deficiency, and responds to administration of vitamin D in any form.[4 5] The vitamin D deficiency is probably multifactorial. It might be anticipated that hydroxylation in the liver would be deficient but this seems rarely to be the case.[6] Malabsorption of vitamin D, especially in cholestatic disease, is a possible factor.[7 8] Lack of exposure to sunlight may be a factor in severely ill patients.[9] Abnormal metabolism of vitamin D or its metabolites seems to play a part in hepatic osteomalacia.[7] Recent attention has centred much more on osteoporosis because osteomalacia is a generalised disease and is readily diagnosed and can be successfully treated.

The pathogenesis of osteoporosis in liver disease is not understood but many factors have been invoked.[10] Hypogonadism and cirrhosis[11] are independent predictors of osteoporosis. Indeed hypogonadism was strongly associated with osteoporosis in patients with idiopathic haemochromatosis.[12] Chronic intestinal malabsorption of calcium may induce hepatic osteoporosis.[13 14] Inactivity, and especially bed rest as a consequence of severe liver disease also contribute to osteoporosis. Alcohol ingestion is also a factor in osteoporosis.[15 16] Steroid treatment is a well authenticated cause of osteoporosis.[17] Corticosteroid therapy reduces bone mineral density in patients with autoimmune chronic active hepatitis[18 19] and primary biliary cirrhosis.[20 21]

Studies in mixed populations with chronic liver disease[11 22] show reduced bone mineral density in 29–39% of patients and the prevalence rate of spinal and peripheral fractures is twice as high in patients with chronic liver disease as in controls.[11] Primary biliary cirrhosis is a paradigm of chronic cholestasis, can be diagnosed early in its course, and thus can be studied sequentially and is the condition par excellence for which liver transplantation is used successfully. Studies of the bones in the early stages of the disease show essentially normal findings,[23] and show that the effects of one year of steroid use cause increased bone loss.[20] Cross sectional surveys show poor correlation of reduced bone mineral density with duration of disease, liver function or previous steroid treatment.[24] None the less, osteoporosis is more prevalent in postmenopausal women with primary biliary cirhossis, and in some studies in those with a prolonged duration of disease.[14] Longitudinal measurements of bone mineral density improve with vitamin D and calcium supplements either alone[25] or with adjuvant calcitonin therapy,[26] presumably by reducing bone resorption. The principal mechanism for hepatic osteoporosis is probably reduced bone formation due to impaired osteoblast function,[27 28] although increased bone resorption may also contribute.[27]

Thus, some patients undergoing liver transplantation have marked pre-existing bone disease, which may be accentuated by factors, such as prolonged bed rest and immobilisation.[29] Immunosuppression, particularly corticosteroid therapy, also contributes to a reduction in bone mineral density.[30] Furthermore, both cyclosporine A[31-33] and tacrolimus[33] increase bone resorption in animal models leading to a loss of trabecular bone. Cardiac transplant patients have cyclosporine associated osteoporosis.[34 35] However, good graft function after liver transplantation should perhaps, overcome the osteoporotic effects of the underlying liver disease. Unfortunately, the initial studies of bone disease after liver transplantation were not encouraging. Haagsma and colleagues,[36] demonstrated vertebral collapse in more than one in three patients despite comparatively minor bone disease pre-operatively and treatment with a vitamin D analogue and supplementary calcium postoperatively. This contrasts with kidney transplantation, which is sometimes followed by avascular bone necrosis principally of the femoral head, but infrequently by generalised osteoporosis. Secondary hyperparathyroidism in chronic renal disease after transplantation may explain this difference. However, secondary hyperparathyroidism is also associated with chronic liver disease.[37] Haagsma *et al*[36] suggested that the pre-existing bone disease in liver transplant recipients was a major factor in the development of bone disease but in their patients another major factor may have been the postoperative dose of corticosteroid immunosuppression as they were treated with 200 mg of prednisolone/day reducing to 40 mg/day after one month and 20 mg/day at one year – high doses of corticosteroids compared with current regimens.

Porayko and coworkers[38] showed an early fall in lumbar spine bone mineral density three months after transplantation, particularly in patients with cholestatic liver disease (primary biliary cirrhosis or primary sclerosing cholangitis) because their values before transplantation were much lower than those of patients with chronic active hepatitis or other liver diseases. After three months, however, bone mineral density in cholestatic liver disease improved whereas that in the other liver diseases continued to deteriorate for up to two years. They also noted avascular bone necrosis in patients with cholestatic liver disease undergoing liver transplantation. Further analysis[39] showed that, in women with primary biliary cirrhosis, lumbar spine bone mineral density was inversely related to the severity of liver disease and the mean rate of bone loss was double that in normal women. This study confirmed the loss of bone mineral density in the lumbar spine in the first three months after liver transplantation with 65% of patients sustaining atraumatic fractures. Perhaps related osteoporosis and bone fracture may have been secondary to the high dose corticosteroid used in the immunosuppressive regimen. When the dose of prednisolone was reduced to 10 mg/day after six months, there was a gradual reversal of bone deficit and bone mineral density had recovered to the pre-operative level by about 12 months

and above the pre-operative level by two years. Furthermore, osteoporosis in this group may have been exaggerated because 38% of patients had amenorrhoea secondary to natural menopause or oophorectomy. An early fall in bone mineral density within three to six months, which thereafter remained stable in most patients up to 36 months, after liver transplantation was confirmed by Arnold and colleagues.[40] They also found a high rate (31%) of atraumatic bone fracture, mainly in the first 12 months after transplantation.

Argao *et al* considered the role of vitamin D supplementation in the recovery of post-transplant bone disease.[41] All their infants and children with chronic cholestasis had subnormal bone mineral content before transplantation. Bone mineral content increased in all patients after transplantation. There was an initial decrease in bone mineral content up to about three or four months after operation in half of the patients with a corresponding fall in serum vitamin D values, suggesting a role for vitamin D supplementation. There was no correlation in individual patients between the change in serum vitamin D level and the change in bone mineral density.

When patients before and one year after liver transplantation[42] are compared there is a high (30%) incidence of vertebral fractures but no difference in bone mass. Longitudinal studies, however, showed significant differences with clear cut losses in spinal bone mineral density and total body bone mineral content. This highlights a potential problem in cross sectional studies where the assumption is made that comparisons are valid. In practice the type of liver disease, the stage of liver disease, the management of transplantation, and the post-transplant drug treatment may vary. This could account for the lack of correlation between the reduction in bone mineral density and factors such as duration and dose of corticosteroid immunosuppression after transplantation found in a cross sectional study of 71 patients from Spain.[43]

Studies from Spain[44] suggested the problems of bone loss after transplantation were less severe than those reported by others.[36 39 40 42] In 82 patients undergoing liver transplantation 41% were osteoporotic as defined by a bone mineral density of more than 2 SD below the mean for normal matched subjects. Although measurements of serum bone markers suggested increased bone loss and high bone turnover, there was no reduction in bone mineral density, nor any clinical or radiological evidence of vertebral collapse or hip fractures or radiological osteonecrosis in the hip after transplantation. This impression of fewer problems with bone disease after liver transplantation in recent years accords with our own studies.[45] In an earlier communication we concluded that, after orthotopic liver transplantation, patients are at an increased risk for the development of severe osteoporosis[45] and found a significant detriment in spinal bone mineral density not only in patients with cholestatic liver disease, but also in those with chronic active hepatitis and cryptogenic cirrhosis prior to transplantation. Patients after transplantation had the most severe osteoporosis of all. However, in our more recent studies[46] we found that severe osteoporosis before liver transplantation was uncommon. Furthermore, in contrast with other studies after transplantation, there was only a marginal fall in femoral neck bone mineral density in the short-term, and in the longterm bone mineral density improved after transplantation.

The pathogenesis of reduced bone mineral density after transplantation is unclear. Bone histomorphometric studies before, and three months after, transplantation suggested increased bone formation by osteoblasts.[47] This was associated with a rise in serum osteocalcin, a vitamin

K dependent protein, synthesised by osteoblasts and distinct from collagen, which is regarded as an index of bone turnover. However the spinal bone mineral density decreased in the first three months after liver transplantation with no further decrease at 12 months. Because histomorphometric studies were not performed during the initial three months after transplantation it is unclear whether increased bone resorption or reduced bone formation was responsible for bone loss. Bone loss was related to the duration of hospital stay (and thus immobility), with no correlation with the dose of corticosteroids or cyclosporine. The increase in osteocalcin after transplantation has been reported in patients with primary biliary cirrhosis.[48] However, there was no clear relation between osteocalcin and the time since transplantation. The authors speculated that the rise in osteocalcin may have been secondary to cyclosporine treatment. The role of osteocalcin in the pathogenesis of bone disease after transplantation is further complicated by the effect of vitamin K deficiency on osteocalcin levels.[49]

What lessons can be learned from these studies of bone disease after liver transplantation? There is abundant evidence that chronic liver disease, particularly of the cholestatic variety, is associated with a diminution in bone mineral density and the risk of atraumatic fractures. This problem is related both to the type of liver disease and its severity. In some circumstances in the few months after liver transplantation bone disease can deteriorate with an increase in the prevalence of atraumatic fractures. This is not a universal finding and is probably becoming less of a problem. A number of factors are involved. Firstly, the severity of disease at the time of referral to a transplant centre may be less now than it was even a few years ago. Patients may be transplanted at an earlier stage when the liver disease and bone disease is less severe. Changing indications for transplantations, for example lethargy, pruritus or portal hypertension, when the parenchymal liver disease is less severe may all play a part. In this context it is notable that there is a well defined subgroup of patients with primary biliary cirrhosis in whom portal hypertension is the dominant feature, indications of the severity of hepatocellular parenchymal disease being less marked.[50] Finally postoperative regimens are changing. Patients now spend much less time in intensive care and as inpatients and postoperative mobilisation is more rapid. The immunosuppressive regimens have changed with less reliance on corticosteroids and this may well be a further factor in minimising bone disease.

Precise details of studies must be scrutinised carefully to ensure that only justified conclusions are drawn and the problem of bone disease has highlighted the defects in cross sectional studies in relation to an evolving form of treatment such as liver transplantation.

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