THORAX

Editorials

Osteoporosis and cystic fibrosis

In the past, cystic fibrosis was a disease of children with a high early mortality resulting predominantly from lung infection. The pulmonary disease therefore took the centre of the stage in terms of treatment and investigations. Now that people with cystic fibrosis are living so much longer, more attention needs to be given to the other organs which may be directly or secondarily affected by the disease. Diabetes occurs in 10% or more, and while it used to be thought that this was relatively mild without vascular complications, evidence to the contrary is beginning to accumulate. Similarly, liver disease has been clinically important in only a small minority, but hepatic complications may progress and become increasingly important in the third and fourth decades. Dietary problems were commonplace in the early days of cystic fibrosis, but have improved for two reasons. In the first place dietary advice has radically altered from low to high fat with high caloric energy—as much as 150% of usual requirements—and this approach has been helped by the development of much more effective pancreatic replacement therapy. Secondly, vitamin supplements have become a routine part of the management of cystic fibrosis and so specific vitamin deficiencies are no longer seen. The report of osteoporosis in this issue of *Thorax* is therefore particularly important as it draws attention to a previously unrecognised problem that may be quite common and may increase as patients survive longer.

In the pathogenesis of osteoporosis, the peak bone density reached at maturity is as important as the ultimate bone loss, and it has recently been restated that "senile osteoporosis is a paediatric disease."[1] The age at which peak bone density occurs is undefined, but it is probably reached by the end of the second decade. In cystic fibrosis Grey and colleagues (p 589) have shown clearly that the skeletons of young adults with an average age of 23 years are significantly compromised in this respect. Patients had a mean bone mineral deficit of 7–13% depending on the bones measured. How comparatively severe is this? Many studies indicate that, at the menopause when bone mineral density (BMD) closely approximates peak values, two standard deviations (SD) span 20% of BMD above and below the mean.[2] In normal subjects each SD below average more than doubles the risk of osteoporotic fracture at any given age.[3,4] In the young this risk should be slight, yet 31% of those with cystic fibrosis had established osteoporotic fractures of the thoracic spine. Only their total body BMD spanned 20% of the control range; individual skeletal sites spanned 30–40%. The distribution of BMD in cystic fibrosis is therefore abnormal, presumably reflecting primary disease severity, and patients appear to be at greater risk of osteoporosis than their mean mineral deficit suggests. It will be important in the future to identify those who are at risk by bone densitometry measurements in childhood.

The authors considered several possible pathogenetic factors, including vitamin and mineral malabsorption, hypogonadism, malnutrition, and relative inactivity. Two apparently independent significant correlates emerged—body mass index and "disease severity" (scored predominantly by pulmonary criteria). These and other aspects deserve further discussion. The time scale of developing osteoporosis remains uncertain; older techniques suggested that BMD is normal in children with cystic fibrosis while quantitative computed tomography revealed a 10% deficit in spinal BMD by the age of 12 on average.[5] Longitudinal studies are now desirable to distinguish further the pathogenetic mechanism and to establish preventive measures.

General nutrition appears to be important but has not been widely studied.[6] Severe deficits in BMD are seen in adolescents with anorexia nervosa and bulimia. Many studies have concentrated on calcium intake with varying results, but its importance is widely accepted.[1,2,7] The recommended dietary intake of calcium during childhood is 1200 mg daily in the USA but this is rarely met. Metabolic balance data collected from around the world indicate that calcium retention during growth is significantly less with intakes below the range of 960–1300 mg daily.[7] Calcium intake is significantly correlated with BMD in British men but not women, possibly because intake in the latter fluctuates much more widely during different periods of life.[2] By several criteria, therefore, a mean (SD) calcium intake of 625 (330) mg daily among patients with cystic fibrosis may be inadequate, even without considering the additional effects of intestinal malabsorption. No correlation between intake and BMD emerged in this study, but it is likely to have had insufficient statistical power. Certainly there seems to be a strong case for fortification of dietary calcium in patients with cystic fibrosis.

It remains unclear as to whether delayed puberty may contribute to osteopenia in cystic fibrosis, as has recently been shown in the general male population.[8] The finding of normal sex hormone levels among (ultimately) mature patients in this present survey does not answer the question. Forearm BMD in men has been found to be predictable by an index of free testosterone (and anthropometric techniques).[2] Weight bearing physical activity is also a determinant of bone density in children,[9] and patients with cystic fibrosis may well suffer in this respect.

The lung disease itself may conceivably have a part to play, other than the chronic sepsis and adverse cytokine influences on bone resorption which Grey *et al* postulate. There is preliminary evidence that chronic obstructive airways disease shows a significant correlation between BMD and forced expiratory volume, even among patients who have never received corticosteroid treatment.[10] BMD was not correlated with oxygen or carbon dioxide tensions. Just as differences in BMD exist at different skeletal sites, so the possibility of relative differences in BMD between the lumbar and thoracic spine needs to be considered, although methods for distin-

guishing them are presently limited. Current international therapeutic trials in postmenopausal osteoporosis exclude "multiple minor wedging of thoracic vertebrae in emphysema" as criteria of "established" osteoporosis. All thoracic crush fractures are likely to affect pulmonary function and reserve among chronic chest sufferers, and this could equally affect prognosis in patients with cystic fibrosis. There is clearly a fertile field for research into all these aspects.

Cystic fibrosis appears to be unique among malabsorption syndromes in the absence of rickets and osteomalacia as a reported complication, even in earlier literature when vitamin D supplementation may have been less widely used. While Hahn *et al*[11] reported lowered levels of serum and urine calcium and of serum 25-hydroxyvitamin D, and raised levels of parathyroid hormone despite small vitamin D supplements, no values were in the range likely to lead to rickets. The findings in the present study, including the achievement of normal adult height, confirm the adequacy of vitamin D nutrition in patients with cystic fibrosis, although continued multivitamin supplementation should remain a simple precaution.

It will clearly be important to confirm and extend these observations and to see how commonly osteoporosis occurs in other age groups. A number of other important questions will need to be addressed. In the first place, the clinical consequences are unclear. Secondly, we need to know whether the poor bone mineralisation can be reversed with treatment. Thirdly, the use of systemic or inhaled steroids in cystic fibrosis is becoming more widespread and this may make the problem worse. Furthermore, it will be important to know the true benefit of adding prophylactic calcium supplements to the diets of people who already have to take a formidable number of tablets every day. It may be some consolation to realise that the patients who have been the subject of this study may well have had a low fat diet for much of their early life and are not, therefore, typical of the next cohort of patients with cystic fibrosis whose nutrition throughout life should be very much better. The paper is a useful and helpful reminder to those looking after patients with cystic fibrosis, in particular respiratory physicians, that there is more to the condition than the lungs alone and to emphasise the cardinal importance of adequate nutrition.

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