

BONE MINERALISATION IN CYSTIC FIBROSIS



Report of the UK Cystic Fibrosis Trust Bone Mineralisation Working Group

February 2007

The UK Cystic Fibrosis Trust Bone Mineralisation Working Group

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The Working Group would like to thank:

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Mr Alan Larsen, Director of Research and Finance at the Cystic Fibrosis Trust
Jacqueline Ali, Publications Officer at the Cystic Fibrosis Trust



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Grading scheme for recommendations used in Bone Mineralisation in Cystic Fibrosis

The criteria for the grading of recommendations in this document are based upon a paper by Petrie et al published on behalf of the Scottish Intercollegiate Guidelines Network.

Much of the data in the document are derived from observational studies where randomisation is not appropriate or possible but many are from peer reviewed scientific studies therefore this grading is not always appropriate.

Grading of recommendations

| <i>Grade</i> | <i>Type of recommendation (based on AHCPR, 1992)</i> |
|--------------|--|
| A | Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation. |
| B | Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation. |
| C | Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality. |

Petrie GJ, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. *Clinical guidelines: criteria for appraisal for national use*. Edinburgh: Royal College of Physicians, 1995.

Agency for Health Care Policy and Research. *Acute pain management, operative or medical procedures and trauma 92-0032. Clinical practice guidelines*. Rockville, Maryland, USA: Agency for Healthcare Policy and Research Publications, 1992.

SUMMARY

- People with cystic fibrosis (CF) may develop low bone mineral density (BMD) from either osteoporosis or vitamin D deficiency osteomalacia.
- Osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.
- Osteomalacia is a disorder where there is an increase in the proportion of non-mineralised bone.
- The World Health Organisation (WHO) working definition of osteoporosis, a lumbar spine and/or hip BMD value, measured by dual energy x-ray absorptiometry (DXA), ≥ 2.5 SD below the young adult mean (T-score), has only been validated in postmenopausal women. In other groups the relationship between BMD and fracture risk has not been established. For this reason, the use of the term osteoporosis in the context of CF should be confined to those with a history of fragility fracture. We suggest that the term “CF-related low BMD” be applied to children or adults with CF with a BMD Z-score below -2 , (< 2 SDs below the age and gender matched mean reference value) with the caveat that Z-scores may be unreliable in individuals of small body size.
- BMD values should be expressed as Z-scores in premenopausal women and in men under 50 years of age and as T-scores thereafter.
- Interpretation of DXA scan BMD values in children, adolescents and small adults is particularly complex because of the effect of bone size on the value obtained. DXA scans calculate the cross-sectional area of the scanned bone and thus measure areal rather than true volumetric density. This does not appear to be a problem in clinical practice in adult CF care, but DXA scans may underestimate BMD in children with CF who have suboptimal growth and short, narrow bones. There are several methods suggested for adjusting BMD and bone mineral content (BMC) for factors such as body size, pubertal stage, skeletal maturity and body composition, but currently there is no consensus on the optimum method to use. If adjustments are made, the method used should be clearly stated in the report. In addition, robust reference data for children and adolescents groups are limited.
- DXA scans should be performed in CF Centres with the appropriate expertise to properly interpret the results.
- BMD is generally normal in children with CF who have well preserved lung function and nutrition. Reduction in BMD Z-scores may appear around puberty, and approximately one third of adults with CF have low BMD.
- Although the pathophysiology of low BMD in people with CF has not been wholly defined, both increased bone resorption and decreased bone formation have been described.
- CF-related low BMD has a multifactorial aetiology including malnutrition, vitamin D and vitamin K insufficiency, calcium deficiency, reduced levels of weight-bearing activity, glucocorticoid use, delayed puberty, hypogonadism, CF-related liver disease (CFRLD), CF-related diabetes mellitus (CFRD) and the systemic inflammatory response to pulmonary infection.

- Significant correlates of BMD include FEV₁%, intravenous antibiotic requirements, glucocorticoid usage, body mass index (BMI), CFRD, parathyroid hormone (PTH) levels, physical activity, and testosterone, oestradiol, and c-reactive protein (CRP) levels.
- It is unclear whether there is a link between bone pathology and the cystic fibrosis transmembrane regulator (CFTR) gene mutation.
- Fracture data in people with CF are limited but suggest an increased prevalence of rib and vertebral fractures in adults. These may inhibit effective airway clearance leading to a decline in lung function. In addition, some lung transplant centres consider low BMD and/or fragility fracture a contraindication to transplant listing.
- The central principles for preventing and treating low BMD-associated fracture are heightened surveillance through screening for low BMD and fragility fracture, and the optimisation of clinically modifiable factors that are likely to affect bone health.
- Children with CF should have DXA BMD measurements in the lumbar spine and proximal femur at about ten years of age. DXA scans should be repeated every one to three years thereafter determined by clinical need to ensure that bone accrual is occurring at a satisfactory rate. Serial measurements allow the identification of peak bone mass, following which bone-sparing treatments can be considered if premature bone loss occurs.
- Chest x-rays should be examined specifically for vertebral fractures. Lateral thoracic and lumbar spine x-rays should not be performed routinely due to the relatively high radiation dose involved, but should be performed in patients judged at risk of fragility fracture based on clinical and DXA findings.
- Good nutrition is vital. Vitamin D and vitamin K status, calcium intake and lean body mass should be optimised through frequent liaison with a specialist CF dietitian. Vitamin D and calcium levels should be measured at least annually. Specialist dietetic supervision of appropriate and proactive interventions with oral calorie supplements and enteral tube feeds is fundamental to care. Patients should have access to a specialist dietitian at each outpatient review, inpatient admission, and at the annual assessment.
- Vitamin D supplementation should be individualised with the aim of achieving serum 25 hydroxyvitamin D (25OHD) levels between 30 and 60 ng/ml (75–150 nmol/L).
- Patients with CF should as a minimum achieve the reference nutrient intake (RNI) for calcium though intakes of 1300–1500 mg/day have been suggested in those over eight years of age.
- Treatments to prevent the progression of lung disease should be optimised due to the likely negative impact of pulmonary infection/systemic inflammation on bone health.
- Weight-bearing physical activity should be encouraged and liaison with a specialist CF physiotherapist is advisable to develop an exercise programme appropriate to each individual's abilities and needs.
- Glucocorticoid treatment should be kept to a minimum.

- Pubertal delay or hypogonadism should be recognised and treated. Pubertal development should be assessed from about eight to nine years of age in girls and 10 to 11 years in boys. Morning serum testosterone levels should be measured annually in adolescent/adult males and a menstrual history should be taken annually in adolescent/adult females to screen for hypogonadism. An endocrinology referral should be considered for patients with pubertal delay, hypogonadism or poor growth.
- Where appropriate, advice should be given about the deleterious skeletal effects of smoking and alcohol abuse.
- Bisphosphonate treatment in adults should be considered when:
 - *The patient has sustained a fragility fracture.*
 - *The lumbar spine or total hip or femoral neck Z-score is <-2 and there is evidence of significant bone loss (>4%/year) on serial DXA measurements despite implementation of the general measures to optimise bone health.*
 - *The patient is starting a prolonged (greater than three months) course of oral glucocorticoid treatment and has a BMD Z-score of <-1.5.*
 - *The patient is listed for or has received a solid organ transplant and has a BMD Z-score of <-1.5.*
 - *Calcium and vitamin D supplements should be routinely co-prescribed with bisphosphonates.*
- Bisphosphonates are contra-indicated in pregnancy and should therefore be used with caution in premenopausal women.
- We recommend that treatment of children with bisphosphonates is supervised by a specialist CF Centre or by a paediatric bone specialist.
- Bisphosphonates are not licensed for use in children and although they appear to be relatively safe even when used for long periods in other paediatric bone disease, experience is limited. There are no published data reporting the outcome of bisphosphonate use in children with CF. However, bisphosphonates may be beneficial in children with a history of fragility fracture and those listed for/post transplantation. Some authorities suggest bisphosphonates for children who have low BMD and continuing bone loss despite implementing general measures for optimising bone health.
- Patients treated with bisphosphonates should initially be monitored with repeat DXA at six to twelve monthly intervals.

I. NORMAL BONE PHYSIOLOGY

The skeleton serves to provide a rigid framework for the body, providing a site for attachment of muscles, housing the bone marrow and protecting the internal organs. It also acts as a reservoir of calcium and phosphate ions and plays a major role in calcium and phosphate homeostasis.

I.1 The composition of bone

Bone consists of an extracellular matrix, composed mainly of type 1 collagen, proteoglycans and non-collagenous proteins including osteocalcin, osteonectin, matrix GLA protein and cell attachment proteins such as osteopontin and bone sialoproteins. It also contains a number of growth factors that have an important role in bone modelling and remodelling. These include transforming growth factors, insulin-like growth factors and bone morphogenetic proteins. Bone mineral is composed mainly of calcium hydroxyapatite.

I.2 Bone structure

At a macroscopic level there are two types of bone, cortical and cancellous. Cortical or compact bone forms approximately 80–90% of the skeleton and is found mainly in the shafts of long bones and surfaces of flat bones. Cortical bone is laid down concentrically around central canals or Haversian systems, which contain blood vessels, nerves and lymphatic vessels. Cancellous bone consists of interconnecting plates and bars, within which lies the bone marrow and is found mainly in the inner part of flat bones and at the ends of long bones.

At a microscopic level, bone may be either woven or lamellar. Woven bone is formed in the growing skeleton and in some disease states and is characterised by the random orientation of collagen fibres and non-uniform size and distribution of osteocytes. In lamellar bone, the collagen fibres are arranged in parallel bundles.

I.3 Bone cells

The three types of bone cells are osteoblasts, osteoclasts and osteocytes. However, other cell types in the bone microenvironment play a vital role in the production of osteogenic precursor cells and the regulation of bone remodelling.

Osteoblasts are derived from pluripotent stromal stem cells (Owen, 1985) and are responsible for the formation of bone matrix and its subsequent mineralisation. Some osteoblasts subsequently undergo terminal differentiation to become osteocytes, whilst others may become lining cells or die by apoptosis.

Osteoclasts are large, typically multinucleated cells that resorb mineralised bone. They are derived from haematopoietic precursors of the monocyte/macrophage lineage and are formed by the fusion of monocytic precursors (Teitelbaum, 2000).

Osteocytes are small, flattened cells which are embedded within the bone matrix and are connected to each other and to lining cells on the bone surface by a canalicular network that contains the bone extracellular fluid. They play a vital role in bone modelling and remodelling, acting as mechanosensors and initiating the appropriate osteogenic response (Erich & Lanyon, 2002).

1.4 Bone modelling and remodelling

Bone modelling is the process by which skeletal growth and shaping occurs during childhood and adolescence. It is influenced by a number of factors including physical activity, nutrition, and hormonal status. Bone formation initially occurs in the young skeleton through endochondral or intramembranous ossification. Subsequent modelling activity is achieved by the co-ordinated activity of osteoblasts and osteoclasts.

Bone remodelling describes a process by which old bone is removed and subsequently replaced by new bone (Parfitt, 1984). It occurs in the adult skeleton and results in the turnover of approximately 10% of the skeleton per annum. It is a surface based event in which osteoclasts first remove a quantum of mineralised bone followed by the formation, in the cavity created, of osteoid by osteoblasts. The final phase of the remodelling cycle involves the mineralisation of osteoid, a function that is also performed by osteoblasts. Under normal circumstances the temporal sequence is always that of resorption followed by formation. This is referred to as coupling. In the young adult skeleton, the amounts of bone resorbed and formed are quantitatively similar (remodelling balance). Each bone remodelling cycle takes approximately four to six months to complete (Eriksen, 1986).

1.5 Regulation of bone remodelling

The control of bone remodelling is complex and involves the interaction of mechanical stresses, systemic hormones and locally produced factors. The latter, which are produced by bone cells and cells in the bone microenvironment act in a paracrine or autocrine manner and mediate the effects of mechanical and systemic stimuli.

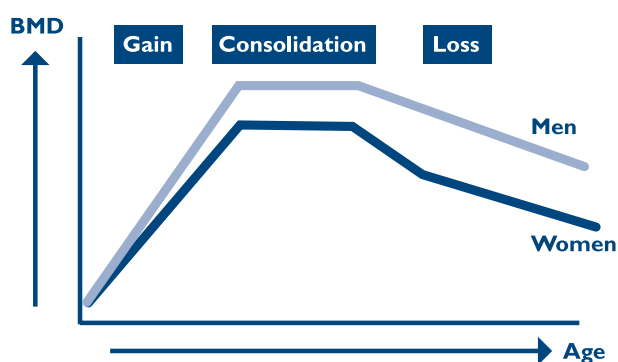
Of the many local factors that have been shown to influence bone resorption, receptor activator of NF kappa B ligand (RANKL) and osteoprotegerin (OPG) are of particular importance (Hofbauer et al, 2000). RANKL is expressed by a number of cell types, including T cells and osteoblastic cells, and interacts with the RANK receptor on osteoclast precursors to stimulate both the development and activity of osteoclasts. OPG acts as a soluble decoy receptor, binding with and inactivating RANKL. Other local factors that are important in the regulation of bone resorption include interleukins 1 and 6, tumour necrosis factors, macrophage-colony stimulating factor and interferon gamma (Compston, 2001).

1.6 Lifetime changes in bone mass

During childhood and adolescence there is rapid linear and appositional skeletal growth. Peak bone mass is achieved in the first part of the third decade and is an important determinant of bone mass thereafter. Approximately 60–70% of variance in peak bone mass is determined by genetic factors (Ralston, 1997). In addition physical activity, nutrition and hormonal status contribute to variations in peak bone mass. Thus increased levels of weight-bearing exercise in adolescents and young adults increase BMD and bone size, whilst immobilisation has adverse effects on bone mass. The influence of nutrition operates both through BMI and the effects of specific nutrients such as calcium and vitamin D. Finally, hypogonadism in both genders reduces bone accretion and may result in failure to achieve normal peak bone mass.

The onset of bone loss occurs at the beginning of the fifth decade or even earlier. However, the cessation of ovarian function at the menopause in women is associated with a phase of rapid bone loss, which probably lasts between five and ten years. Thereafter, bone loss continues at a lower rate and, as in men, continues throughout life (Figure 1). Overall, it is estimated that approximately 50% of cancellous bone and 35% of cortical bone are lost over a lifetime in women, with losses in men of around two-thirds of these amounts (Riggs et al, 1986).

Lifetime changes in bone mass



Oestrogen deficiency is a major pathogenetic factor in age-related bone loss, both in men and women (Riggs et al, 1998a). In addition vitamin D insufficiency, which is common in the elderly population, results in secondary hyperparathyroidism and increased bone loss, predominantly at cortical sites. Reduced levels of physical activity and a reduction in the ability of bone to sense mechanical strains also contribute.

1.7 Mechanisms of bone loss

At the tissue level, bone loss may occur as a result of increased bone turnover and/or remodelling imbalance (Compston, 2001). Increased bone turnover is caused by increased osteoclastic activity, resulting in increased numbers of bone remodelling units on the bone surface. As a result of coupling, bone formation subsequently increases and thus this mechanism of bone loss is potentially reversible. However, because of the increased number of resorption cavities present on the bone surface at any one time, there is an increased risk of trabecular penetration and hence the adverse effects on bone strength are disproportionate for the reduction in bone mass.

Within individual bone remodelling units, remodelling imbalance may occur as a result of increased depth of resorption by osteoclasts, reduced bone formation by osteoblasts or a combination of these two. A negative remodelling imbalance is often associated with increased bone turnover and this combination is characteristic of menopausal bone loss (Vedi et al, 1996).

Bone loss also has structural consequences, both in cortical and cancellous bone (Croucher et al, 1994). Thus as noted above, high bone turnover states may be associated with trabecular penetration and reduction in connectivity of the bone structure. An increased depth of resorption within individual remodelling units will have similar effects. In contrast, low bone turnover and reduced bone formation within remodelling units will predispose to trabecular thinning, with relative preservation of microarchitecture, although thinning itself will eventually predispose to trabecular penetration once the thickness of a trabeculum has been reduced to that of a normal resorption cavity.

In cortical bone the consequences of bone loss are cortical thinning, an increase in porosity and trabecularisation of the endocortical surface of the cortex. These changes make an important contribution to increased bone fragility, particularly at sites rich in cortical bone.

2. CLINICAL CHARACTERISTICS AND PATHOGENESIS OF CYSTIC FIBROSIS-RELATED LOW BONE MINERAL DENSITY

Part of this chapter has previously been published in the European Respiratory Journal Monograph:

C.S. Haworth, S.L. Elkin. Diagnosis and management of cystic fibrosis-related low bone mineral density. In: Cystic Fibrosis. Eur Respir Mon 2006; ERM 35:150–168.

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2.1 Fracture

The prevalence of fragility fractures in children and adults with CF remains unclear. There are no published reports with robust control data of fracture rates in large unselected populations of people with CF.

There have been a number of case reports of fragility fractures that had devastating clinical consequences (Haworth et al, 1999a; Lim et al, 2003; Latzin et al, 2005) and a number of studies reporting population based fracture rates. Henderson and Specter reported that females with CF aged between six and 16 years had higher fractures rates than controls or male patients with CF (Henderson & Specter, 1994). Elkin and colleagues reported that 35% of adults had a history of fracture, 9% of which were rib fractures (Elkin et al, 2001). Aris and colleagues reported fracture rates two fold higher in women aged 16–34 years and in men aged 25–45 years (Aris et al, 1998). Rib and vertebral fractures were particularly prevalent being 10 and 100 fold more common than in the general population. This study reported a particularly high vertebral fracture rate, possibly as a consequence of the participants having end stage lung disease. In this series the majority of the vertebral wedge fractures were relatively mild, with 60% of the fractures resulting in height loss of 10–25%. Six percent of fractures resulted in height loss of >40%.

Rib and vertebral fractures are particularly relevant in people with CF because they can be associated with a rapid decline in lung function, either through causing a pneumothorax or by inhibiting effective sputum clearance. Vertebral fracture, vertebral deformity and kyphosis can lead to a reduction in forced vital capacity and reduced ventilatory efficiency. Some centres also view fragility fracture and/or low BMD as a relative contraindication to lung transplantation.

It is unclear how much the increased fracture rate in current adult cohorts is a consequence of the standard of nutritional and pulmonary care available two decades ago. Advances in all aspects of CF care may now allow more normal bone development and lead to a reduced incidence of fracture in the future. However, for the current generation of adults, fracture rates are likely to increase as they grow older as a result of the normal age-related bone loss, unless bone sparing treatments are given.

2.2 Bone mineral density in people with cystic fibrosis

Reduced BMD was first described in patients with CF in 1979 (Mischler et al, 1979; Hahn et al, 1979) but the full extent of the problem was not realised until the 1990s when several cross sectional BMD studies were performed. Hardin and Sood and colleagues (Hardin et al, 2001a; Sood et al, 2001) reported on small numbers (13 and 29) of well children with CF. Controls were matched for body size as well as age and gender. No differences in bone mineral status were seen between children with CF and controls, suggesting that well children with CF have smaller, but normally mineralised bones. These results should be viewed with caution, probably applying only to relatively healthy and well nourished children with CF, but are supported by the study of Buntain and colleagues (Buntain et al, 2004).

Three specialist CF Centres in the UK have performed detailed prevalence studies. The Manchester Centre reported that 34% (48/143) of adults had a BMD Z-score of -2 or less in the lumbar spine, proximal femur or distal forearm (Haworth et al, 1999b). The Leeds Centre reported that 66% of 114 patients had osteopenia or osteoporosis defined by WHO criteria using T-scores (Conway et al, 2000). The Royal Brompton Hospital reported that 38% of 107 patients had Z-scores of -1 or less, with 13% having Z-scores of -2 or less (Elkin et al, 2001).

Buntain and colleagues performed a controlled cross sectional study involving 153 people with CF and 149 local healthy controls. They found normal BMD in children with CF, normal axial BMD (after adjustment for height) in adolescents with CF, but a significant reduction in BMD in adults with CF (Buntain et al, 2004).

Bhudhikanok and colleagues studied 41 patients aged nine to 50 years (Bhudhikanok et al, 1998). BMD increased by 1–2% per year in axial sites, except in adult men ($n=6$) who experienced a 1.2% reduction in the femoral neck. The BMD Z-scores of the younger patients decreased with age suggesting that age-related increases were less than those expected in normal age matched controls.

Haworth and colleagues prospectively measured the BMD of 114 adults with CF (Haworth et al, 2002). In 55 patients with a mean age of 19 years, in whom BMD would normally be expected to increase annually before reaching peak bone mass, BMD was stable in the lumbar spine but decreased by more than 2% per year in the proximal femur. In 59 patients with a mean age of 30 years, in whom BMD would normally be expected to remain stable having achieved peak bone mass, there were no significant changes in the lumbar spine but there were significant annual reductions in BMD in the proximal femur (-1.5%) and distal forearm (-0.8%).

Collectively, these studies suggest BMD is within normal limits in well-nourished children with preserved lung function, but many patients fail to gain bone normally and/or experience premature bone loss in adolescent/early adult life.

2.3 Bone turnover markers

Most studies measuring serum and urinary bone turnover markers indicate that adult patients with CF have a combination of accelerated bone breakdown and inadequate bone formation.

Baroncelli and colleagues investigated 59 patients and 72 age and sex matched controls and found increased values of serum cross-linked carboxy-terminal telopeptide of type 1 collagen and urinary values of cross-linked N-telopeptides of type 1 collagen in prepubertal children, pubertal children and young adults with CF, suggesting that patients with CF have increased levels of bone resorption (Baroncelli et al, 1997). The reduced levels of osteocalcin and carboxy-terminal propeptide of type 1 procollagen in pubertal patients and the reduced values of osteocalcin in young adult patients suggests that reduced bone formation also contributes to disordered bone metabolism in CF.

Aris and colleagues measured bone turnover markers in 50 clinically stable adults with CF and 53 matched controls (Aris et al, 2002). Patients with CF had higher urinary N-telopeptides of type 1 collagen and free deoxypyridinoline levels than controls. Serum osteocalcin levels were similar in the two groups. These results suggest that adults with CF have increased bone resorption with relatively normal levels of bone formation.

Greer and colleagues measured bone turnover markers in 149 patients with CF and 141 controls (Greer et al, 2003). The ratio of osteocalcin to urinary total deoxypyridinoline was similar in CF and control children, but decreased in adolescents and adults with CF, suggesting bone accretion was reduced relative to resorption in adolescents and adults with CF.

2.4 Bone histomorphometry

Bone histomorphometry characterises the alterations in bone structure and remodelling found in bone diseases. In CF, it is also useful to confirm or refute the presence of osteomalacia. Histological evidence of osteomalacia appears to be rare in CF, although reports have documented osteomalacia in iliac crest biopsies of two adult patients with CF, both of which were associated with low serum 25OHD levels and raised serum PTH (Friedman et al, 1985; Elkin et al, 2002).

Haworth and colleagues reported an analysis of autopsy bone samples from 15 patients with CF and 15 young adult controls (Haworth et al, 2000). Eleven of the patients had had transplants and had received immunosuppressive medications. Cortical and trabecular bone volume was reduced and at the cellular level there was evidence of decreased osteoblastic and increased osteoclastic activity. The latter changes resulted in an increase in resorptive surfaces. However, in the absence of tetracycline labelling dynamic indices of bone formation and resorption could not be assessed.

Elkin and colleagues reported an analysis of bone histomorphometry from tetracycline labelled iliac crest samples taken from adults with CF with low BMD measured by DXA (Elkin et al, 2001). The results revealed lower cancellous bone area and a significantly lower bone formation rate at both tissue and cellular level when compared to samples taken from age and gender matched controls. Resorption was decreased in the people with CF as a whole, although there was considerable heterogeneity in the measurements. The mineralisation lag time was increased and the mineral apposition rate decreased in people with CF indicating a mild mineralisation defect.

These studies indicate that reduced bone formation plays an important role in low BMD associated with CF, although it is likely that increased bone resorption also occurs intermittently, possibly during periods of ill health/infection.

2.5 Aetiology and risk factors for CF-related low bone mineral density

The aetiology of CF-related low bone mineral density is multifactorial. The major risk factors are discussed below.

2.5.1 Influence of cystic fibrosis transmembrane conductance regulator protein

Different authorities argue for and against a direct link between CF-related low BMD and CFTR dysfunction, with most large cross sectional studies showing no association between CF genotype and low BMD (Aris et al, 1998; Haworth et al, 1999b; Conway et al, 2000; Elkin et al, 2001; Buntain et al, 2004).

Nevertheless, King and colleagues reported lower BMD in patients with the delta F508 mutation (King et al, 2005). Haworth and colleagues reported significant differences in bone turnover between delta F508 homozygotes and non-homozygotes (Haworth et al, 1999b) but found no significant difference in the annual reduction in bone mass between delta F508 homozygotes and non-homozygotes (Haworth et al, 2002).

Dif and colleagues performed a histomorphometric analysis of the bones of CF knockout mice (Dif et al, 2004). The CFTR mutants displayed a significant (50%) reduction of cortical bone width and thinner trabeculae. Analysis of dynamic parameters indicated a significant reduction in bone formation and increased bone resorption. The absence of pulmonary disease suggests that other processes contributed to the pathogenesis of low BMD in these mice.

2.5.2 Disease severity and proinflammatory cytokines

Numerous cross-sectional studies in people with CF have shown that low BMD is associated with disease severity as represented by FEV₁, BMI, number of intravenous antibiotics days and exercise tolerance (Aris et al, 1998; Bhudhikanok et al, 1998; Haworth et al, 1999b; Conway et al, 2000; Elkin et al, 2001; Haworth et al, 2002; Buntain et al, 2004). Severely ill patients and those waiting for transplantation invariably have low BMD (Aris et al, 1996; Donovan et al, 1998). Those patients with normal BMI and good lung function appear to have near normal bone density (Hardin et al, 2001a).

Acute pulmonary infection in CF is associated with increased circulating levels of interleukin 6 (IL-6), interleukin 1 (IL-1) and tumour necrosis factor (TNF) alpha. These cytokines are also known to increase osteoclast formation and activity (Manolagas & Jilka, 1995). Evidence that systemic inflammation may play a role in bone loss was first reported in 1999 when Haworth and colleagues demonstrated an inverse correlation between serum CRP and DXA Z-scores (Haworth et al, 1999b). Ionescu and colleagues showed that BMD in 22 adults with CF was related to FEV₁ and to levels of IL-6 and TNF alpha soluble receptors (Ionescu et al, 2000). In addition, Aris and colleagues demonstrated that urinary N-telopeptides and serum IL-1, IL-6 and TNF alpha levels fell and that osteocalcin levels rose in patients with CF following antibiotic treatment for infective exacerbations (Aris et al, 2000a). In a one year longitudinal study of 100 adults with CF, Haworth and colleagues showed that serum IL-6 levels were an independent predictor of the annual change in BMC and were related to urinary levels of N-telopeptide cross-links, further suggesting a pathophysiological link between systemic inflammation and bone loss in CF (Haworth et al, 2004a).

2.5.3 Nutritional factors affecting bone physiology

Many aspects of nutrition affect bone remodelling, including vitamins, minerals, protein intake and acid load. In the following section vitamin D, vitamin K and calcium will be considered.

a) Vitamin D

Reduced sunlight exposure in CF, (due to illness, hospitalisation or through advice regarding photosensitivity from antibiotic therapy) and the malabsorption of fat-soluble vitamins place individuals with CF at high risk of hypovitaminosis D.

The two main forms of vitamin D are ergocalciferol (vitamin D₂) and colecalciferol (vitamin D₃). The latter is derived from sunlight exposure when the precursor 7-dehydrocholesterol absorbs ultraviolet (UV) B light. Under normal circumstances cutaneous synthesis is the main source of vitamin D. Only a minority of vitamin D comes from dietary intake (Holick, 2002). Fish liver oils e.g., cod liver oil and fatty fish such as herring, mackerel, pilchard, sardines and tuna are rich sources of the vitamin but are not usually major contributors to the diet. Other sources are eggs and fortified foods.

The absorption of vitamin D is dependent on bile salts and the lymphatic transport system. After synthesis in the skin or absorption from food, vitamin D is transported to the liver where it is hydroxylated to 25OHD, the major circulating form of the vitamin. Serum 25OHD levels are a good indicator of vitamin D status. In the kidney, 25OHD undergoes further hydroxylation to the major active metabolite 1, 25 dihydroxyvitamin D (1,25(OH)₂D). Serum 1,25(OH)₂D levels may be significantly lower in CF (Greer et al, 2003) suggesting the possible importance of normally functioning renal CFTR for normal renal 1 α -hydroxylase activity.

1, 25 dihydroxyvitamin D synthesis is stimulated by PTH, hypocalcaemia and hypophosphataemia. The physiological effect of 1,25(OH)₂D is to maintain normal plasma calcium levels, mainly by increasing calcium absorption from the intestine but also by stimulating osteoclastic bone resorption and hence releasing calcium and phosphate from bone into the circulation. Low levels of 1,25(OH)₂D increase the production of PTH, resulting in increased bone turnover and bone loss, particularly in cortical bone.

Severe prolonged vitamin D deficiency results in osteomalacia (adults) or rickets (children), conditions characterised by defective mineralisation of bone. More commonly, lesser degrees of deficiency, termed insufficiency, result in secondary hyperparathyroidism and increased bone loss, particularly in cortical bone. The definition of vitamin D insufficiency is controversial but a minimum desirable serum 25OHD level of 28 to 32 ng/ml or 70 to 80 nmol/L (median 30 ng/ml or 75 nmol/L) has been suggested (Dawson-Hughes et al, 2005). The CF Foundation Consensus Group on Bone Health and Disease in CF recommended that serum 25OHD levels >30 ng/ml (75 nmol/L) are necessary to optimise bone health (Aris et al, 2005). This figure was selected because in non-CF individuals serum PTH levels rise when serum 25OHD levels fall below this threshold. Recently, Boyle and colleagues (Boyle et al, 2005a) investigated a group of 111 patients with CF and found 65.8% had levels <30 ng/ml (75 nmol/L). These individuals had significantly higher serum PTH levels (>50pg/ml) than those individuals with serum 25OHD >30 ng/ml (75 nmol/L).

Vitamin D absorption appears to vary considerably amongst individuals with CF. Lark and colleagues reported that adults with CF absorbed less than one-half of a single dose of oral vitamin D₂ in comparison to non-CF controls (Lark et al, 2001). Serum 25OHD levels in people with CF as a whole did not rise in response to vitamin D₂, in contrast to the control group which showed a doubling of serum 25OHD levels. However, there was a wide variability in the individual absorption curves of people with CF with three exceeding the mean absorption of the control group.

Although overt evidence of vitamin D deficiency is rare in CF (Friedman et al, 1985; Elkin et al, 2002) an early study reported a 36% reduction in 25OHD concentrations with a significant reduction in serum calcium levels and secondary hyperparathyroidism (Hahn et al, 1979). The reported prevalence of low serum 25OHD levels varies considerably according to the diagnostic criteria used (Ott & Aitkin, 1998). However three large adult studies from the UK reported remarkably similar serum 25OHD levels. Haworth and colleagues found that 53/139 (38%) adults with CF had 25OHD levels <15 ng/ml (37.5 nmol/L) despite supplementation with 900IU vitamin D/day (Haworth et al, 1999b); Conway and colleagues reported that 39.8% of adolescents and adults had levels <15 ng/ml (37.5 nmol/L) despite supplementation with ~800IU vitamin D/day (Conway et al, 2000). Elkin and colleagues reported that 36% of adults with CF had levels <10 ng/ml (<25 nmol/L) (Elkin et al, 2001).

Studies in children suggest that low serum 25OHD levels are uncommon (Grey et al, 2000; Chavasse et al, 2004; Buntain et al, 2004), although these studies are limited by the lack of agreement about normal ranges in healthy children.

Despite many reports of a high prevalence of vitamin D insufficiency, most studies have not found a correlation between serum 25OHD levels and BMD (Aris et al, 1998; Haworth et al, 1999b; Conway et al, 2000; Elkin et al, 2001; Buntain et al, 2004). Buntain and colleagues reported a significant BMD deficit in the presence of vitamin D sufficiency in a large Australian cohort suggesting that low BMD in CF can occur independently of vitamin D insufficiency (Buntain et al, 2004). The relative role of vitamin D insufficiency in the pathogenesis of low BMD in CF therefore remains unclear. However, it is highly probable that low serum 25OHD levels contribute to the loss of bone by causing intermittent secondary hyperparathyroidism and a consequent increase in bone turnover. This may well occur during the winter and spring months when serum levels will be at their lowest and PTH levels are at their highest. Consistent with this hypothesis, Haworth and colleagues reported a negative relationship between mean BMD Z-score and serum PTH in 139 adults with CF (Haworth et al, 1999b). A later study reported significantly lower levels of serum 25OHD and a trend towards a higher mean serum PTH in a group of adults with CF compared to age and sex matched controls (Aris et al, 2002).

b) Calcium

Calcium is required for normal growth, development and maintenance of the skeleton. About 99 per cent of the total body calcium is present in the form of hydroxyapatite or bone mineral. Requirements vary throughout life, with greater calcium needs during periods of rapid growth such as in infancy and during the pubertal growth spurt in adolescence. Calcium supplementation in children and adults has been shown to have beneficial effects on BMD (Riggs et al, 1998b; Matkovic et al, 2005; Dodiuk-Gad et al, 2005; Vatanparast & Whiting, 2006). Calcium homeostasis is controlled by PTH and 1,25(OH)₂D, the former acting to increase distal tubular renal calcium reabsorption and bone resorption and the latter to increase intestinal calcium absorption. PTH-induced effects are important in short-term adjustments in calcium homeostasis, whereas stimulation of the synthesis of 1,25(OH)₂D by PTH, with a subsequent increase in intestinal calcium absorption, provides longer-term regulatory control.

Calcium intake is a positive predictor of bone mineral status in adolescents with CF (Chan et al, 2001). Low mean serum calcium levels have been reported in CF (Aris et al, 1999). Individuals are at risk of a negative calcium balance from poor dietary calcium intake. Although most studies report good mean calcium intakes (Kawchak et al, 1996; Haworth et al, 1999b; Conway et al, 2000; Mortensen et al, 2000), more than half of adolescent females with CF do not meet current recommended intakes (Schulze et al, 2003a).

Other risk factors for a negative calcium balance include vitamin D insufficiency (Haworth et al, 1999b; Conway et al, 2000; Elkin et al, 2001), gastrointestinal malabsorption that may not be fully corrected by pancreatic enzyme replacement therapy (Aris et al, 1999), and increased endogenous faecal loss (Schulze et al, 2003b). Gastric acid increases the solubility of calcium salts. The use of proton pump inhibitors to increase the efficacy of pancreatic enzyme replacement therapy may contribute to reduced absorption of calcium in CF.

c) Vitamin K

People with CF are at risk of developing vitamin K deficiency because its absorption from the gut is dependent on bile salt and pancreatic lipase secretion stimulated by dietary fat (Vermeer et al, 1995). Other risk factors include liver disease, frequent antibiotic therapy, inadequate dietary intake and in some, short gut syndrome resulting from bowel resection (Durie, 1994). Unlike the other fat soluble vitamins, vitamin K is not routinely supplemented in CF clinics in the UK.

Vitamin K acts as a co-factor for gamma-carboxylation of osteocalcin and other bone matrix proteins, a step necessary for their binding to bone mineral (Suttie, 1992).

Clinicians are guided by secondary and insensitive indicators of vitamin K deficiency, e.g., the prothrombin time, as direct measurements of serum or urinary vitamin K levels are not routinely available. Undercarboxylated osteocalcin is the most accurate method of assessing vitamin K adequacy for bone metabolism but is used mainly as a research tool. However, manifestations of vitamin K deficiency in liver and bone may occur independently, (Vermeer et al, 1998; Mosler et al, 2003). Vitamin K status should be considered in relation to individual tissues (Vermeer et al, 1998).

There is growing evidence that many patients with CF have inadequate levels of vitamin K. Recent studies have shown that vitamin K deficiency is common in children with CF, and particularly in patients who are pancreatic insufficient or who have CFRLD.

In 1999 Rashid and colleagues performed a prospective study investigating vitamin K metabolism in 98 patients with CF and 62 healthy controls (Rashid et al, 1999). All patients with CFRLD and 78% of pancreatic insufficient patients had raised PIVKA-II (proteins induced in vitamin K absence) levels.

Aris and colleagues measured total and carboxylated osteocalcin in 52 patients with CF and found the carboxylated levels to be lower compared to non-CF controls (Aris et al, 2003). Although there was a moderate association between carboxylated osteocalcin and both the prothrombin time and the lumbar spine BMD T-score, no direct measurement of vitamin K was performed.

Conway and colleagues found similar results in a group of 93 children with CF (Conway et al, 2005). Serum vitamin K levels showed a significant negative correlation with undercarboxylated osteocalcin levels but showed no correlation with any marker of bone turnover. Undercarboxylated osteocalcin levels were significantly correlated with bone turnover markers, which themselves showed a significant negative correlation with measurements of BMD and BMC. There were, however, no significant correlations between carboxylated or undercarboxylated osteocalcin levels and bone density measurements.

2.5.4 Glucocorticoids

Glucocorticoids cause rapid bone loss, especially during the first year of therapy. They inhibit gastrointestinal calcium absorption and increase renal calcium excretion, possibly leading to an increase in PTH production. Osteoblast recruitment from osteoprogenitor cells is decreased and there is accelerated apoptosis of osteoblasts. Bone resorption is increased both as a result of increased production of RANKL relative to osteoprotegerin (OPG) and because of hypogonadism. The overall affect is to increase the number of sites undergoing remodelling but with decreased bone formation at these sites.

Most of the larger cross sectional studies in individuals with CF have demonstrated an association between oral glucocorticoid usage and low BMD. Aris and colleagues found that the cumulative dose of glucocorticoids was a predictor of BMD in people with CF awaiting transplantation (Aris et al, 1998). Bhudhikanok and colleagues reported that glucocorticoid use in CF was associated with significantly lower BMD Z-scores at the femoral neck and lumbar spine (Bhudhikanok et al, 1998). Conway and colleagues found that oral glucocorticoid use was independently associated with decreased BMD in the lumbar spine and femoral neck, and inhaled glucocorticoids with reduced total body BMD (Conway et al, 2000). Elkin and colleagues reported a negative correlation between oral glucocorticoid use and femoral neck Z-score (Elkin et al, 2001). In a longitudinal study, the oral glucocorticoid dose was inversely related to change in BMD in the lumbar spine and proximal femur (Haworth et al, 2002).

2.5.5 Physical activity

There is no direct evidence that lack of weight-bearing exercise leads to low BMD in individuals with CF. However, a number of studies have found a correlation between physical activity and BMD, particularly in the axial skeleton (Bhudhikanok et al, 1998; Haworth et al, 1999b; Conway et al, 2000; Elkin et al, 2001; Haworth et al, 2002). At present it is unknown if weight-bearing exercise in people with CF can increase peak bone mass, preserve BMD or increase BMD in those with low BMD.

2.5.6 Delayed puberty and hypogonadism

In normal populations, peak height velocity occurs at 11.7 years (Tanner stage 3) in girls and 13.4 years (Tanner stage 4) in boys. There is a significant negative relationship between age at menarche and peak bone mineral content velocity (PBMCV), with the greatest bone mineral content accrual over the two year period around PBMCV in early maturing girls and the least accrual in late maturing girls (McKay et al, 1998).

Despite most children with CF achieving normal or near normal growth, puberty may be delayed (Johannesson et al, 1997; Arrigo et al, 2003; Ujhelyi et al, 2004) and is associated with a reduction in bone age (Leifke et al, 2003). Peak height velocity has been shown to be delayed by nine to 10 months in boys and 10 -14 months in girls with CF (Patel et al, 2003).

Data concerning secondary hypogonadism in adult males with CF are conflicting with some groups reporting normal testosterone levels (Haworth et al, 1999b; Conway et al, 2000) and others low levels (Elkin et al, 2001), possibly as a result of the use of different methods of assessment. Elkin and colleagues reported that 31 of 58 males had low total serum testosterone, 18% also having a low free testosterone level (Elkin et al, 2001). The latter significantly correlated with total body BMD.

Rossini and colleagues investigated 191 adults with CF (100 men) and found that serum oestradiol levels were below the normal range in 23% of females and 27% of males (Rossini et al, 2004). Serum oestradiol was significantly related to femur BMD values in men and women. Men with prevalent vertebral fractures had significantly lower serum oestradiol levels than patients without fractures. Free testosterone levels were within the normal range in all males but they were significantly lower in patients with prevalent vertebral fractures than in other patients.

3. BONE DENSITOMETRY IN CYSTIC FIBROSIS

BMD can be measured using a variety of techniques including dual energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT) and ultrasound.

3.1 Dual energy X-ray absorptiometry scans

Dual energy x-ray absorptiometry (DXA) is used to measure BMD in the lumbar spine, proximal femur, distal radius and whole body. DXA is a projection technique that provides a 2-D image of the region scanned. The density is calculated by measuring the bone mineral content (BMC) of the bones (based on attenuation coefficient analysis of each pixel), calculating the projected area occupied by the bone pixels and dividing the BMC by the area to give the areal density (aBMD).

The precision of DXA measurements (measure of the repeatability of the method) in the lumbar spine, proximal femur and total body is approximately 0.6%, 1.5% and 0.8% respectively in adults (Oldroyd et al, 2003). It is important to take in to account the precision of the measurement when deciding whether a change in BMD is significant.

The scan time of fan beam scanners is approximately two to three minutes per site and involves a low effective radiation dose (effective dose usually <1 mSv per site). For comparison, the effective dose of naturally occurring background radiation is 6-20mSv per day in the UK and the effective dose of a chest x-ray is 20mSv.

Manufacturers differ in the facilities they offer for scanning the axial skeleton in children. GE Lunar initially only offered lumbar spine scanning although newer versions of software may include femur scan options, whilst Hologic offer both spine and femur scan modes for children. GE Lunar do not routinely offer femur scanning as femoral geometry changes during growth.

It should be emphasised that DXA provides an areal density (g/cm^2) rather than a true volumetric density (g/cm^3), since the scans are two-dimensional. The interpretation of areal BMD therefore poses major challenges in healthy children due to changes in bone size related to age and puberty, and in children with chronic diseases in whom poor growth and pubertal delay adversely affect bone size. As a consequence, some groups have questioned whether bone mineral deficits truly occur in patients with CF or whether the differences observed between patients and controls are size related (Laursen et al, 2000; Sood et al, 2001; Hardin et al, 2001a). In addition to size dependence, longitudinal measurements of BMD may also be influenced by changes in body composition.

Various methods have been suggested for adjusting BMD and BMC for factors such as body size, pubertal stage, skeletal maturity and body composition, but currently there is no consensus on the optimum method to use (see appendix A and National Osteoporosis Society publication "A practical guide to bone densitometry in children," 2004).

3.2 Quantitative computed tomography scans

Quantitative computed tomography (QCT) provides separate measures of cortical and trabecular BMD and can be used to measure BMD in the axial and peripheral skeleton. QCT measures the volumetric density (g/cm^3) and so the results are not influenced by body size. As trabecular bone is considerably more metabolically active than cortical bone, QCT can be more sensitive than DXA at detecting small changes in BMD.

The disadvantages of QCT are its higher cost and higher radiation dose (effective dose 55 mSv in the lumbar spine) compared to DXA. It is also less precise than DXA with axial coefficients of variation of 1–3%.

3.3 Quantitative ultrasound

Measurements obtained by quantitative ultrasound (QUS) are based upon the attenuation of the ultrasound beam as it passes through the specified region of interest in peripheral skeletal sites, most commonly broadband ultrasound attenuation or speed of sound. These are thought not only to be related to the mineral density of bone but also to reflect parameters of bone quality and strength. At the present time, most ultrasound scanners are applied to the calcaneus, which is predominantly trabecular bone. QUS does not involve ionising radiation and the scanners are generally portable and so can be used in the community. QUS has limited application in monitoring change in skeletal status because its precision in the calcaneus is worse than that of DXA or QCT (SOS = 4.3 – 8.4%; BUA = 2.8-6.9%) (NOS, 2004). Body height and therefore bone size strongly influence QUS results which should be interpreted with consideration of anthropometric measurements (Fricke et al, 2005). QUS is not recommended for routine clinical use.

3.4 Bone mineral density software and reference data

Meaningful interpretation of bone densitometry data is reliant upon having robust normative data, which should ideally be specific for sex, ethnic origin, and pubertal status. Height and weight should also be taken in to account.

Most centres in the UK use reference data supplied by densitometer manufacturers. DXA has the largest reference data and smaller databases are available for QCT and QUS. The reference data for all techniques are less reliable for children than for adults, and some paediatric reference databases combine gender and ethnic groups. Some centres have developed locally derived reference data to overcome this problem or use data published in the literature, but these databases often include insufficient subjects to be truly representative. Furthermore, some reference databases include data derived from scanners and software that are now out of date. Thus, the quality of the reference data can significantly affect the standard deviation score of a BMD measurement.

3.5 Bone mineral density data: Z- and T- scores

BMD results are compared to reference populations and reported as standard deviation scores from the mean. The Z-score is the standard deviation score from the mean BMD of an age and gender matched control population. The T-score is the standard deviation score from the mean BMD of a control population of gender matched young adults at peak bone mass. Peak bone mass is normally achieved during the third decade of life, at which time Z- and T-scores are similar.

The purpose of performing bone densitometry is to identify individuals who are at risk of developing a fragility fracture. However, the relationship between BMD and fracture risk has not been established in CF and the WHO working definition of osteoporosis based on bone density T-scores has only been validated in postmenopausal women (WHO, 1994). For this reason, the term osteoporosis should be avoided in people with CF except for those with a history of fragility fracture (or in postmenopausal women diagnosed appropriately using T-scores).

Most adult bone densitometry centres perform DXA measurements in the lumbar spine and proximal femur. Only a few centres routinely perform whole body scans. As paediatric bone densitometry centres often utilise techniques to normalise BMD for body size and perform BMD measurements in the lumbar spine and whole body, this may lead to difficulties in continuity of monitoring when the child transfers to the adult service. This discontinuity may prove to be particularly confusing as a change from paediatric to adult reference values may produce changes in diagnostic categorisation.

3.5.1 Recommendations for the interpretation of bone densitometry results in children with CF

The National Osteoporosis Society has recently produced recommendations for interpretation of paediatric DXA scans (NOS, 2004). Our recommendations have been based upon their report:

The most widely used bone density technique currently applied to children in clinical diagnosis is DXA, and the following comments apply to this method:

- *BMD should be measured in the lumbar spine (and proximal femur, if available) from about 10 years of age [C].*
- *Z-scores should be used in children. T-scores must not be used in children [C].*
- *Z-scores must be interpreted in the light of the best available paediatric reference database of age-matched controls. The reference database used should be cited in the report [C].*
- *The diagnosis of osteoporosis in children with CF should not be made on the basis of densitometric criteria alone. Terminology such as “low bone density for chronological age” may be used if the Z- score is below -2 , with the caveat that unadjusted Z-scores may be unreliable in individuals of small body size [C].*
- *There are several methods suggested for adjusting BMD and BMC for factors such as body size, pubertal stage, skeletal maturity and body composition, but currently there is no consensus on the optimum method to use. If adjustments are made the method used should be clearly stated in the report [C].*
- *Serial BMD scans should be performed on the same machine using the same scanning mode, software and analysis when appropriate [C].*
- *Any deviation from standard adult acquisition protocols, such as the use of low-density software and manual adjustment of the region of interest, should be stated in the report [C].*
- *It is recommended that bone density scans should ideally be performed in centres with a clinical team that has expertise in bone densitometry in children [C].*
- *It is important to note that the predictive value of BMD for fractures in children is not yet determined.*

3.5.2 Recommendations for the interpretation of bone densitometry results in adults with CF

The National Osteoporosis Society has recently produced recommendations for interpretation of paediatric DXA scans (NOS, 2004). Our recommendations for bone densitometry in adults with CF have been based upon the report in children because of the problems of interpreting DXA data in people with small bones. The most widely used bone density technique currently applied to adults in clinical diagnosis is DXA, and the following comments apply to this method:

- *Proximal femur BMD measurements in addition to lumbar spine BMD measurements should be performed in early adulthood (after bone growth has stopped). The total hip measurement and reference data derived from the third US National Health and Nutritional Examination Survey (NHANES III, 1997) should be used to interpret BMD in the proximal femur [C].*

- *BMD values should be expressed as Z-scores in premenopausal women and in men under 50 years of age, and as T-scores thereafter [C].*
- *As the WHO working definition of osteoporosis based on bone densitometry T-scores has only been validated in postmenopausal women (WHO, 1994), the term osteoporosis should be avoided in people with CF except for those with a history of fragility fracture (or in postmenopausal women diagnosed appropriately using T- scores). The term “low BMD” may be used in individuals with a BMD Z-score below -2 , with the caveat that unadjusted Z-scores may be unreliable in individuals of small body size [C].*
- *There are several methods for adjusting BMD and BMC for factors such as body size and body composition, but currently there is no consensus on the optimum method to use. If adjustments are made the method used should be clearly stated in the report [C].*
- *Serial BMD scans should be performed on the same machine using the same scanning mode, software and analysis when appropriate [C].*
- *Any deviation from standard adult acquisition protocols, such as the use of low-density software and manual adjustment of the region of interest, should be stated in the report [C].*
- *The predictive value of BMD for fractures in young adults is not yet determined.*

4. MANAGEMENT OF CF-RELATED LOW BONE MINERAL DENSITY

Part of this chapter has previously been published in the European Respiratory Journal Monograph:

C.S. Haworth, S.L. Elkin. Diagnosis and management of cystic fibrosis-related low bone mineral density. In: Cystic Fibrosis. Eur Respir Mon 2006; ERM 35:150–168.

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4.1 Principles for prevention and treatment of low bone mineral density

The central principles for preventing and treating low BMD are heightened surveillance through screening for low BMD and fragility fracture, and the optimisation of clinically modifiable factors that are likely to affect bone health.

4.2 Bone densitometry and screening for fragility fractures

Due to the uncertainties surrounding interpretation of BMD results in children, the optimal age for commencing DXA screening is unclear. Some authorities suggest performing DXA from eight years of age if risk factors for low BMD have been identified (Aris et al, 2005), while an alternative view is that DXA might only be appropriate when individuals have stopped growing (Buntain et al, 2004).

4.2.1 Recommendations

- *A DXA scan should be performed from about 10 years of age and repeated every one to three years, determined by clinical need, to ensure that bone accrual is occurring at a satisfactory rate. Serial measures will allow the identification of peak bone mass, following which bone-sparing treatments can be considered if premature bone loss occurs [C].*
- *DXA scans should be performed and interpreted according to the bone densitometry recommendations outlined in the previous chapter [C].*
- *Chest x-rays should be examined specifically for evidence of vertebral fractures. Lateral thoracic and lumbar spine x-rays should not be performed regularly in every patient due to the relatively high radiation dose involved, but should be performed in patients judged at risk of fragility fracture based on clinical and DXA findings [C].*

4.3 General measures to optimise bone health

4.3.1 Recommendations

- *As problems with bone health in adults are likely to have their origins in childhood, it is extremely important for paediatric care workers to optimise factors that are likely to affect bone health in the future and for adult care workers to continue these management principles after transition [C].*

- *A specialist CF dietitian should actively participate in the continued assessment and management of people with CF. The primary aim of nutritional management is to achieve normal weight, height, rate of growth and body composition (CF Trust, 2002a). Energy and protein requirements are highest at the time of peak growth and adequate intakes of all nutrients are essential. Maintenance of an optimal BMI particularly during the pubertal growth spurt is a key treatment aim (Aris et al, 2005) [C].*
- *Regular dietetic counselling focussing on optimising energy intakes and other nutrients that support bone development should be available to patients. Nutritional management includes encouraging a high-fat diet, with appropriate pancreatic enzyme replacement therapy (PERT) to maximise energy intakes. The use of oral dietary supplements may benefit some patients. Others may require additional nutritional support through enteral tube feeding. The definitions of growth failure, criteria for staged nutritional intervention and treatment strategies have been extensively reviewed (Borowitz et al, 2002; Sinaasappel et al, 2002; CF Trust, 2002a) [C].*
- *Vitamin D levels, vitamin K intake, calcium intake and lean body mass should be optimised through regular liaison with a specialist CF dietitian [C].*
- *Weight-bearing physical activity should be encouraged. A specialist CF physiotherapist should develop an exercise programme appropriate to each individual's abilities and needs. (Appendix B) [C].*
- *Glucocorticoid treatment should be kept to a minimum [C].*
- *Pubertal delay or hypogonadism should be recognised and treated [C].*
- *Where appropriate, advice should be given about the deleterious effects of smoking and alcohol on BMD [C].*
- *Treatments to prevent the progression of lung disease should be optimised due to the likely negative impact of pulmonary infection/systemic inflammation on bone health [C].*

4.4 Vitamin D supplementation

There are no trials of vitamin D supplementation alone on bone health in children or adults with CF.

Oral vitamin D supplementation (800IU/day for four to ten weeks) failed to achieve 25OHD levels above 13.3 nmol/L (5.3 ng/ml) (the winter lower limit of normal in this study) in eight of 20 people with CF (Hanly et al, 1985).

Oral ergocalciferol (1800IU/day) achieved a serum 25OHD level >20 ng/ml (50 nmol/L) in 95% of patients with CF (Kelly et al, 2002).

High dose oral ergocalciferol treatment (50,000IU/week for eight weeks) in 66 adults with CF with baseline 25OHD levels <30 ng/ml (75 nmol/L) resulted in five (8%) achieving levels >30 ng/ml (75 nmol/L) (Boyle et al, 2005b). Thirty three patients went on to receive 50,000IU twice weekly for eight weeks, none of whom achieved levels >30 ng/ml (75 nmol/L).

Intramuscular ergocalciferol did not lead to a significant increase in serum 25OHD in adults with CF (Ontjes et al, 2000).

Oral calcitriol (0.5IU twice daily for 14 days) was associated with increased fractional absorption of calcium from the gut, a reduction in PTH levels and a reduction in bone resorption markers in ten adults with CF. However, there was no significant change in serum 1,25(OH)₂D levels (Brown et al, 2003).

During the winter and spring months, serum 25OHD levels may be reduced by 50%. It has been shown in children with CF that the seasonal variation in vitamin D levels can be reduced by close attention to serum 25OHD levels and enhanced supplementation (Wolfe et al, 2001).

In a non-randomised trial investigating the effects of ultraviolet B radiation one to three times per week, mean (95% CI) serum 25OHD levels increased from 24.5 ng/ml (21.8–27.1) to 50.2 ng/ml (45.8–54.7) or 61.3 nmol/L (54.5–67.8) to 125.5 nmol/L (114.5–136.8), ($p < 0.0001$) in ten patients with CF who received UVB treatment for four months (five patients did not complete the intervention). 25OHD levels in the control group ($n=15$) did not alter significantly during the study period (Gronowitz et al, 2003).

The effect of a combined vitamin D and calcium supplement on bone metabolism and bone density was assessed in a one year randomised double blind placebo controlled trial (Haworth et al, 2004b). Patients were randomised to receive Calcichew D₃ Forte two tablets daily (calcium 1000 mg/day and colecalciferol 800IU/day) or placebo, in addition to their standard multivitamin supplements (ergocalciferol 900IU/day). The mean (SD) daily calcium intake before the intervention in the treatment group compared to the control group was 837 (512) mg vs 1077 (506) mg (NS). Although no change in serum 25OHD or PTH levels was demonstrated between groups, the rate of decline in lumbar spine, total hip and distal forearm bone density was less in the treatment group compared to the control group, though these differences did not reach statistical significance.

There have been no trials of additional calcium and vitamin D supplementation in children with CF.

4.4.1 Recommendations

- *25OHD levels should be measured at diagnosis and annually thereafter and following changes in vitamin D dosing, taking into account that there will be seasonal variations [C].*
- *Vitamin D supplementation should be individualised with the aim of achieving serum 25OHD levels between 30 and 60 ng/ml, (75 and 150 nmol/L) [C].*
- *If 25OHD levels are below 10 ng/ml (25 nmol/L) or the serum corrected calcium is below the normal range, PTH levels should be measured. If osteomalacia is suspected, referral to a bone specialist is recommended [C].*
- *If serum 25OHD levels are suboptimal, the patient should be seen by a specialist CF dietitian who will review their dietary intake, the preparation and dose of their vitamin D supplement, the patient's adherence to vitamin D therapy, and will ensure that their supplements are taken at mealtimes with the concurrent administration of pancreatic enzymes to facilitate absorption [C].*
- *Recommended daily doses of ergocalciferol or colecalciferol for routine supplementation in pancreatic insufficient patients are: <1 year, 400IU (10 mcg); 1–12 years, 400–800IU (10–20mcg); >12 years, 800–2000IU (20–50mcg) (CF Trust, 2002a) [C]. Since there is no plain tablet of this strength available it is necessary to give it combined with either vitamin A or calcium.*

- *Considerably higher doses of vitamin D than those suggested above may be required in some patients to achieve adequate serum 25OHD levels (Kelly et al, 2002; Boyle et al, 2005b). As vitamin D is often given in combination preparations containing vitamin A, care should be taken when increasing the dose of the supplement to prevent vitamin A toxicity, which can be detrimental to bone health (Promislow et al, 2002). In these circumstances a separate vitamin D preparation may be required. The most commonly prescribed calcium and vitamin D supplements are described in Table 8.4 [C].*
- *If 25OHD levels do not respond adequately to increased doses of oral ergocalciferol, UVB therapy (Gronowitz et al, 2003), or more polar vitamin D analogues such as calcitriol or alfacalcidol (see Table 8.1) should be considered [C]. The latter will increase 1,25(OH)₂D levels.*

4.5 Calcium intake

The degree of gastrointestinal calcium malabsorption in individual patients with CF is difficult to quantify (Aris et al, 1999). There are no studies of calcium supplementation alone on the effects on bone health in patients with cystic fibrosis.

A number of studies of calcium supplementation in non-CF children and adolescents have shown increased calcium deposition in bone, and improved bone mineral accretion and BMD (Matkovic et al, 2005; Dodiuk-Gad et al, 2005) especially when dairy produce is the source of the calcium (Chan et al, 1995).

4.5.1 Recommendations

- *A specialist CF dietitian should review calcium intake at the annual review [C].*
- *A calcium intake of 1300 to 1500 mg/day from the age of eight years is recommended [C].*
- *If calcium intake is low, dietary calcium intake should be optimised through increased consumption of dairy sources [C].*
- *Plasma calcium levels should be more closely monitored in patients with renal impairment [C].*
- *Calcium may interfere with the absorption of other medicines (particularly bisphosphonates, iron and some antibiotics e.g., ciprofloxacin) and is therefore better taken on its own at a different time of day [C].*
- *Commonly prescribed calcium supplements are listed in Table 8.5 [C].*

4.6 Vitamin K

There are no published randomised controlled trials assessing the effect of vitamin K supplementation on bone metabolism in patients with cystic fibrosis.

There is no clear international consensus on the optimal dosing regimen for patients with CF. As vitamin K is metabolised within 24 hours, (Olsen, 1994) it is likely that a daily dose will be required. Recommendations from the USA, Europe and the UK vary from 0.3–0.5 mg/day (Aris et al, 2005; Borowitz et al, 2002), to 1 mg/day and 10 mg/week, (Sinaasappel et al, 2002) or 10 mg/day (CF Trust, 2002a). The CF Foundation Consensus Statement on Bone Health and Disease recommends that in the absence of data specific to CF vitamin K supplementation should follow the Dietary Reference Intakes (Aris et al, 2005).

4.6.1 Recommendations

- *There is not yet sufficient evidence to recommend universal vitamin K supplementation for bone health in CF, but consideration should be given to individuals with low BMD, liver disease and/or a prolonged prothrombin time [C].*
- *When vitamin K supplements are prescribed we recommend that they should be given as daily phytomenadione (phyloquinone, Vitamin K₁), 10 mg/day for children from seven years of age and adults. We recommend a dose of 300 micrograms/kg/day, rounded to the nearest 1 mg, for babies and infants under two years. For children age two–seven years we recommend a dose of 5 mg/day, using a pill cutter to halve the tablets [C].*
- *Konakion MM[®] Paediatric (2 mg/0.2 ml) can be given orally but involves opening glass ampoules. For infants and young children the unlicensed preparation, Orakay[®] is an alternative. The contents of the capsule can be taken orally by cutting the end of the capsule and squeezing the content into the child's mouth [C].*

4.7 Endocrine issues

Children with CF are at increased risk of protein catabolism which contributes to poor weight gain and growth. There has been recent interest in utilising the anabolic effects of growth hormone in CF to increase bone accretion with significant improvements in bone mineral content, height, weight, lean tissue mass and the number of hospitalisations in prepubertal children with CF (Huseman et al, 1996; Hardin et al, 2001b; Hardin et al, 2001c) including those receiving enteral nutritional support (Hardin et al, 2005). At present, there are insufficient data to recommend its routine use in children with CF-related low BMD, but it is a potential treatment option for those with reduced BMD and short stature.

An uncontrolled trial demonstrated advancement in sexual maturation following intramuscular testosterone in five adolescent males with CF (Landon & Rosenfeld, 1984). There is no evidence supporting the administration of testosterone for treatment of low bone mineral density unless associated with delayed puberty in adolescence or hypogonadism in adult men. There are no studies reporting the effects of oestrogen therapy in adolescent females with CF.

4.7.1 Recommendations

- *Pubertal development should be assessed from the age of about eight to nine years in girls and 11 years in boys. Morning serum testosterone levels should be measured annually in adult males and a menstrual history should be taken annually in adolescent/adult females to screen for hypogonadism [C].*
- *An endocrinology referral should be considered for patients with pubertal delay, hypogonadism or poor growth [C].*

- *An oral glucose tolerance test should be performed annually from 12 years of age to screen for CFRD [C].*
- *As medroxyprogesterone (Depoprovera®) and possibly other progesterone-only preparations have deleterious effects on BMD, particularly in adolescents, alternative contraceptive preparations should be discussed [C].*
- *Growth hormone should only be considered for treatment of children with low bone mineral density in consultation with a paediatric endocrinologist. [C].*

4.8 Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and may also inhibit osteoblast apoptosis. Alendronic acid is licensed in the UK for the prevention and treatment of postmenopausal osteoporosis, treatment of male osteoporosis and the prevention and treatment of glucocorticoid induced osteoporosis. The licensed indications for risedronate are not quite so extensive and for both drugs the licensed indications for the weekly preparations are limited to the treatment of postmenopausal osteoporosis. Intravenous and oral ibandronic acid are also now licensed for the treatment of postmenopausal osteoporosis. Intravenous pamidronate is not licensed for the treatment of osteoporosis in the UK, although it is used for this indication in selected patient groups. There are four published studies to date assessing the effect of bisphosphonates in people with cystic fibrosis, all of which use BMD as the primary endpoint rather than fracture reduction.

The efficacy of intravenous pamidronate was assessed in a randomised controlled trial involving 28 adults with CF with low bone density (Haworth et al, 2001). The treated group received pamidronate 30 mg every three months and both groups received additional calcium (1000 mg/day) and vitamin D (800IU/day). After six months of treatment, the pamidronate group (n=13) showed a significant increase in BMD compared with the control group (n=15) in the lumbar spine (mean difference 5.8%, CI 2.7% to 8.9%) and total hip (mean difference 3.0%, CI 0.3% to 5.6%). Several individuals experienced severe bone pain after each pamidronate infusion but those taking oral glucocorticoids or who had recently completed intravenous antibiotic treatment were asymptomatic, suggesting that these interventions had a protective effect (Haworth et al, 1998; Haworth et al, 1999c). Severe bone pain has also been reported following zoledronic acid therapy (Boyle et al, 2005c). Oral alendronic acid and risedronate can also cause bone discomfort when first used in people with CF, but these effects are usually less severe than those associated with intravenous pamidronate.

The efficacy of alendronic acid (10 mg/daily) was assessed in a one year randomised double blind placebo controlled trial in 48 adults with CF with low bone density (Aris et al, 2004). All patients received colecalciferol 800IU/day and calcium 1000 mg/day. In the alendronic acid group compared to the control group, the mean \pm SD change in bone density was $4.9\pm 3.0\%$ vs $-1.8\pm 4.0\%$ in the lumbar spine ($p<0.001$) and $2.8\pm 3.2\%$ vs $-0.7\pm 4.7\%$ in the femur ($p=0.003$).

In a non-randomised study reporting change in bone density in adults with CF prescribed or not prescribed oral bisphosphonates (alendronic acid or etidronate) for a mean duration of more than two years, the bisphosphonate treated group experienced more favourable changes in bone density in the lumbar spine, femoral neck and total body than untreated subjects (Conway et al, 2004).

The efficacy of intravenous pamidronate (30 mg every three months) was assessed in a two year randomised controlled study in 34 patients with CF after lung transplantation. All subjects received colecalciferol 800IU/day and calcium 1000 mg/day. Those treated with pamidronate gained $8.8 \pm 2.5\%$ and $8.2 \pm 3.8\%$ in the lumbar spine and femur after two years compared to controls who gained 2.6 ± 3.2 and $0.3 \pm 2.2\%$ respectively, ($p \leq 0.015$ for both) (Aris et al, 2000b). Seven and six fractures occurred in the control and pamidronate groups, respectively ($p > 0.2$). None of the patients in this study developed bone pain, reinforcing the suggestion that glucocorticoids reduce the risk of pamidronate associated bone pain in people with CF.

There are no published data reporting outcomes of bisphosphonate use in children with CF.

4.8.1 Recommendations – Adults

- *Bisphosphonate treatment in adults with CF should be considered when:*
 - *The patient has sustained a fragility fracture [C].*
 - *The lumbar spine or total hip or femoral neck Z-score is < -2 and there is evidence of significant bone loss ($> 4\%/year$) on serial DXA measurements despite implementation of the general measures to optimise bone health [C].*
 - *The patient is starting a prolonged (greater than three months) course of oral glucocorticoid treatment and has a BMD Z-score of < -1.5 [C].*
 - *The patient is listed for or has received a solid organ transplant and has a BMD Z-score of < -1.5 [C].*
 - *Calcium and vitamin D supplementation should be routinely co-prescribed with bisphosphonates.*
- *The choice of bisphosphonate should be governed by clinical circumstance and patient preference [C].*
- *Intravenous bisphosphonates can be used to circumvent some of the problems associated with the oral bisphosphonates such as poor oral bioavailability ($< 1\%$ in healthy subjects), upper gastrointestinal intolerance and low adherence [C].*
- *The prescription of prednisolone 20-30 mg/day for three days before administering intravenous pamidronate, or for three days starting on the day before treatment, may prevent/reduce the severity of the bone pain. Alternatively paracetamol or ibuprofen may be prescribed. Tolerance to bisphosphonates often occurs with repeated infusions so that glucocorticoids, paracetamol and ibuprofen can be given at reduced doses and gradually withdrawn [C].*
- *Patients taking oral bisphosphonate preparations should be advised not to take calcium supplements at the same time, as absorption is impaired by calcium [C].*
- *Bisphosphonates should be taken in the fasting state and patients should remain upright for a period after taking the drug to facilitate gastrointestinal absorption of oral bisphosphonates and minimise the risk of oesophageal reactions [C].*
- *The weekly dosing regimens available with alendronic acid and risedronate are likely to be preferable to daily dosing regimens for most patients with CF [C].*

- *Bisphosphonates should not be prescribed in pregnancy and should be used with caution in premenopausal women since they cross the placenta. Even if the drug has been discontinued prior to conception, there is a theoretical risk that it may be released from bone during pregnancy. Thus, bisphosphonates should not be prescribed to women trying to conceive and those who may wish to become pregnant in the future should be counselled about the potential risks of bisphosphonate treatment. Women should be advised to use adequate contraception while taking bisphosphonates and should ensure that they are not pregnant when starting treatment. Risedronate may have a shorter half-life in bone than alendronic acid and so may be a more appropriate choice [C].*
- *The medical records should contain clear documentation of informed consent for bisphosphonate treatment, as CF-related low BMD is not a licensed indication [C].*
- *Bisphosphonates should not be prescribed in patients with osteomalacia. If the serum 25OHD level is <10 ng/ml (25 nmol/L) and the PTH is increased (or the patient has hypocalcaemia), bisphosphonate treatment should be avoided and the patient should be referred to a bone specialist [C].*
- *Bone densitometry measurements should initially be repeated six to 12 months after starting bisphosphonate treatment to assess efficacy. If BMD decreases significantly while prescribed oral bisphosphonates, intravenous pamidronate should be considered [C].*
- *Bisphosphonates should not be prescribed to patients with severe renal impairment (creatinine clearance <30 ml/min) [C].*
- *Renal function, serum corrected calcium, potassium and magnesium levels should be monitored in patients prescribed intravenous aminoglycosides and intravenous bisphosphonates [C].*
- *Oral bisphosphonate should not be prescribed in patients with oesophageal varices (refer to drug data sheets for full list of contraindications) [C].*

4.8.2 Recommendations – Children

- *Bisphosphonates must only be prescribed for children in a specialist CF Centre [C].*
- *Bisphosphonates may be beneficial in children with a history of fragility fracture and those listed for/post transplantation [C].*
- *Bisphosphonates may be indicated in children who have low BMD and continuing bone loss despite implementing the general measures for optimising bone health [C].*

5. MANAGEMENT ADVICE FOR SPECIFIC CLINICAL SCENARIOS

5.1 Airway clearance techniques in patients with CF with low bone mineral density

There is some concern that chest percussion and shaking during airway clearance could cause a rib fracture in this group of patients. Although the Chartered Society of Physiotherapy guidelines for the management of patients with osteoporosis (without CF) state that ‘percussion and shaking are contra-indicated for patients with severe osteoporosis’ (CSP, 1999) there are no reports of manual techniques causing rib fractures during airway clearance in CF. Whilst the risk is theoretical, rib fracture pain may impair the patients’ ability to perform effective airway clearance and reduce mobility. This may lead to an infective exacerbation, hospitalisation and potential irreversible decrease in lung function.

Other methods of airway clearance without the use of manual techniques have proven efficacy and should be considered as alternatives (CF Trust, 2002b). Coughing has been reported to be a cause of rib fracture (Elkin, 2001). A regular review of airway clearance including effective coughing by a specialist CF physiotherapist is particularly important for this group of patients.

5.1.1 Recommendation

- *Care should be taken with some of the manual techniques associated with airway clearance e.g., chest shaking, chest percussion, as there may be an increased risk of rib fracture [C].*

5.2 Management of patients with CF with painful rib or vertebral fractures

Rib and vertebral fractures are often extremely painful in the acute setting and can inhibit effective airway clearance. Patients often need admission to hospital to optimise their clinical care. A chest x-ray should be performed to exclude pneumothorax in patients with a suspected rib fracture.

Effective analgesia is a priority and may be achieved with a combination of paracetamol, non-steroidal anti-inflammatory drugs and tramadol. If this is unsuccessful consider subcutaneous calcitonin, which has been reported as providing rapid pain relief in an adult with CF with a rib fracture and in postmenopausal subjects with vertebral fractures (Jones et al, 2001; Mehta et al, 2003). If this is ineffective, nerve blocks, nitrous oxide and air, or intravenous diamorphine delivered through a patient controlled analgesia pump should be considered. These can be particularly helpful in controlling pain during airway clearance sessions. Careful monitoring is obviously required when these drugs are prescribed to patients with respiratory disease. Non-pharmacological interventions such as trans-cutaneous electrical neural stimulation (TENS) may be of use.

Sputum trapping is frequently associated with painful rib or vertebral fractures so it may be sensible to start intravenous antibiotic therapy. Mucolytic treatment with rhDNase and intravenous aminophylline may also be beneficial in some patients to facilitate sputum expectoration.

5.2.1 Recommendations

- *Pain control is crucial before airway clearance is commenced (see above) [C].*
- *The use of antibiotics and rhDNase are recommended to reduce sputum volume and ease the mobilisation of secretions (see above) [C].*
- *Patients should be instructed how to support the chest wall to facilitate effective coughing [C].*
- *Early mobilisation with adequate pain relief should be encouraged [C].*

5.3 Management of patients with CF starting long term oral glucocorticoids

5.3.1 Recommendations

- *For adults in whom it is intended to continue oral glucocorticoid therapy for at least three months, a Z-score of -1.5 or lower may indicate the need for intervention with a bone-sparing agent, although the effect of age on fracture probability in an individual should be taken in to account when making treatment decisions. There is no evidence base for similar preventative treatment in children.*
- *In adults if the DXA Z-score is above -1.5 at the commencement of oral glucocorticoid therapy a repeat DXA is recommended after six to 12 months[C]. In children a baseline DXA scan should be performed if glucocorticoid treatment is planned for at least three months. A Z-score of -1.5 or lower should prompt a review of possible nutritional, biochemical and hormonal causes with adjustment of therapy where indicated. The DXA scan should be repeated after six months. If further intervention is needed in adults or children this should take into account whether glucocorticoid treatment is continuing and follow the guidelines for bisphosphonate therapy in 4.8.1 and 4.8.2 .*

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APPENDIX A

Dual energy x-ray absorptiometry bone density and body composition adjustment techniques

Carter suggested normalising spine bone mineral content for volume, allowing for differences in skeletal size, to give a truer picture of density (Carter et al, 1992). This value was called bone mineral apparent density. The initial problem was to obtain an estimate for bone volume from the two dimensional DXA image. Utilising allometric scaling techniques (Smith, 1984) they suggested using the spine area (A_p) from the lumbar spine scan raised to a power of 1.5 to produce a volume estimate (V^*). The spine BMC value is then divided by V^* to produce BMAD.

$$V^* = A_p^{1.5} \quad \text{hence} \quad \text{BMAD} = \text{BMC}/V^*.$$

This model was constructed in a group of subjects aged 17–40 years scanned using an Hologic QDR-1000 system, but has been used successfully in a number of paediatric and adult CF studies to compare BMAD with standard aBMD techniques (Bachrach 1994, Bhudhikanok et al, 1996, Conway et al, 2000).

Kroger proposed a volumetric model for the lumbar spine and femoral neck in children that assumed both regions had a cylindrical shape (Kroger et al, 1992). The models were constructed utilising data from paediatric Lunar DPX spine and femur scans (subjects six – 19 years of age). By using parameters readily available from scan output data, they proposed that femur BMAD should be calculated by multiplying aBMD by $4h/\pi A$ where h was the height of measured area in the femoral neck and A was the projected area. Similarly, they proposed that lumbar spine BMAD could be derived by multiplying aBMD by $4/(\pi w)$ where w is the mean width of the vertebrae L2–L4.

$$\text{BMAD} = \text{aBMD} \times 4/(\pi w)$$

This methodology has been used successfully in a number of paediatric studies and Kroger reported that the estimates of volume made from areal DXA scans in adults correlated sufficiently well with MRI volume based corrections to be valid when MRI was not available (Kroger et al, 1995). However, the study only used data from L3.

Crabtree and colleagues demonstrated a strong relationship between lean tissue mass and bone mineralization and showed that when lean tissue mass is used to normalise bone mineral the effects of ethnicity become negligible (Crabtree et al, 2004). However individual reference ranges for the genders are still required.

Little adjusted normative (reference) data is available in which to set these results but work is progressing in the UK to produce these data. Where body size or growth is a factor in monitoring of bone mineralization, methods for normalising for such factors should be used.

Adjustments for total body dual energy x-ray absorptiometry measurements in children

DXA techniques allow a three compartment analysis (bone, fat and lean body mass) of the total body to be made which may be useful for adjusting bone mineral results for body composition. As DXA is a 2D areal assessment of density, the raw BMC values should be treated with caution when body size and growth are compromised. For example, a low BMC result from a total body scan may simply reflect small body size. For these reasons a number of adjustment techniques have been proposed.

Molgaard suggested a three-step method for diagnosing bone problems in children (Molgaard et al, 1997). His models were developed on data collected from children in the age range five to 19 years using an Hologic QDR-1000. They defined the idea of short, narrow or light bones as a method of understanding mineralization in growing children. The first step of the three-stage method was to determine whether height was appropriate for age, with small stature indicating “short bones”. The second step was to estimate whether the bone area derived from the scan was appropriate for height, with a low bone area indicating “narrow bones”. Finally BMC is compared to bone area with a low relative BMC indicating “light bones”. A later paper (Laursen et al, 2000) went on to utilise this method in children with CF and showed that the main reasons for reduced BMC for age were “short”, “narrow” bones.

Schoenau utilised a mechanostat based model (Frost, 1987) for understanding bone mineralization which he proposed was due to the muscle forces exerted on the bone (Schoenau et al, 2002). He therefore suggests using peripheral QCT (pQCT) and correcting bone mineral content for muscle cross sectional area. Their data were collected at the forearm using a Stratec XCT-2000 system. They showed that after BMC was normalised for muscle cross sectional area, that although there were differences between the genders in pubertal status, there was relatively little change within genders. The implications of this work are that adequate muscle mass for height produces adequate BMC and that BMC results should be viewed in this context rather than just using age matched or height matched estimates. They describe an algorithm utilising their results, which as a first step uses muscle mass, normalised for body height, and as a second step uses BMC normalised for muscle cross sectional area. These two steps allow a diagnosis of “normal bone”, “primary, secondary or mixed” bone defects. The main problem with this method is the requirement for pQCT which is not available in the majority of clinical establishments.

More pragmatically, Hogler suggests using DXA whole body scans and correcting BMC for the lean tissue mass value derived from the DXA whole body scan as a surrogate for muscle cross sectional area (Hogler et al, 2003). He then proposes using a four stage diagnostic technique, which is a modified version of Molgaard’s (Molgaard et al, 1997) and Schoenau’s (Schoenau et al, 2002) methods. The four steps start with the determination of BMC or BMD for age, which may be classified as normal or low. The second step assesses height for age giving classes of low, normal or high. Step three compares lean tissue mass to height to give classifications of low or normal. Finally, the BMC to lean tissue mass ratio is examined and again classifications of low or normal are made. This leads to the same final diagnostic classifications as those of Schoenau (Schoenau et al, 2002). This work has been extended and validated by the work of Crabtree (Crabtree et al, 2004), this emphasised the strong relationship between lean tissue mass and bone mineralization.

Leonard compared whole body DXA and pQCT at the tibia (Leonard et al, 2004). Based on this they assert that the best method for normalisation of total body BMC is height which related this normalised value to bone strength and dimensions. They suggest that bone area normalised for height is a better indicator of true bone dimension. They also felt that the use of bone area and lean tissue mass as normalising factors were poor indicators of bone strength, although it should be remembered that this work was carried out in the tibia which is not a routinely measured site.

The inclusion or exclusion of the head in whole body analysis is currently a subject of debate. At five years of age the BMC in the head represents approximately 45–50% of total body BMC although this does reduce to about 20% by age 16 (Taylor et al, 1997). In the paediatric age range, head BMC may dominate whole body BMC measurements and changes in those measurements.

Adjustments for lumbar spine and proximal femur dual energy x-ray absorptiometry measurements in adults

The techniques of Carter and Kroger (Carter et al, 1992; Kroger et al, 1995) described above were validated in adult groups.

It would seem sensible to carry out this type of size adjustment in adult lumbar spine BMD measurements to produce and use BMAD values for adult patients with cystic fibrosis. However this means that adult BMAD reference ranges would need to be generated in order that such results could be set in the appropriate context.

It may be worth considering the method of Kroger (Kroger et al, 1995) for size adjustment of femoral bone mineral as this group of patients are likely to be smaller than their age matched peers. Again this type of analysis would require the development of appropriate reference ranges.

Adjustments for whole body measurements in adults

This scan is not routinely performed but is potentially valuable in the assessment of cortical bone mass (the whole body scan comprises of approximately 80% cortical bone).

Body composition can also be derived from the whole body scan and can be a valuable tool in the assessment of nutritional status in patients with CF. The standard two compartment model of fat free mass (FFM) and fat mass (FM) can be normalised, for body height squared, by expression of these quantities as indices fat free mass index (FFMI) and fat mass index (FMI) in a similar manner to the more frequently used body mass index (BMI). Using whole body scans the methods of Molgaard, Hogler and Crabtree (Molgaard et al, 1997; Hogler et al, 2003; Crabtree et al, 2004) should be evaluated in adults to determine their utility. However these departures will demand the development of comprehensive reference ranges for adults.

APPENDIX B

Bone disease – a physiotherapy perspective

Exercise – a physiotherapy perspective

Currently there are no studies in the literature examining the role of exercise on bone health in CF, but interventions evaluated in the non-CF population may provide guidance. The following perspective is based on studies in the healthy population.

Exercise and bone accretion in healthy children and adolescents

The two critical years for bone growth in children without CF are 11.5–13.5 years (Tanner stages 2–4) for girls and 13.05–15.05 years (Tanner stage 3–5) for boys. It has been suggested that an opportune time to intervene with loading exercise is probably when insulin like growth factor 1 (IGF-1) levels are climbing (Tanner stage 1–2) (MacKelvie et al, 2002).

Exercise intervention studies

A systematic review of weight bearing exercise in healthy children and adolescents (using BMD or BMC by DXA as the primary outcome measure) provides guidance for exercise intervention in CF (MacKelvie et al, 2002).

Exercise in prepubertal children

For pre-pubertal children it would appear that the magnitude of increase in weight bearing activity is more important than the specificity of the intervention (Bradney et al, 1998; Fuchs et al, 2001).

Exercise in early pubertal children

In early puberty high impact activities are important (MacKelvie, 2001).

Exercise post menarche

It appears that post menarche it becomes more difficult to promote bone remodelling.

Recommendations

- *Prepuberty increase in general weight bearing activities 30 minutes 3 x weekly extra to curricular activities [C].*
- *Early puberty weight bearing high impact activities 3.5–5 x body weight 12 minutes 3 x weekly at least seven months [C].*

Exercise in adults with normal bone mineral density

The effect of exercise on bone health in adults with CF is unknown. Healthy population studies have shown that generally pre-menopausal women appear to benefit from high impact activities e.g., skipping and jogging (Basse et al, 1994; Heinonen et al, 1996). Clearly for those patients with CF who are not used to regular exercise the programme should begin with low impact exercise and build up slowly.

Recommendations

- *Exercise programmes should be individualised [C].*
- *High impact activities (2.1–5.6 x body weight) 3 x week for 18 months [C].*
- *For those not used to regular exercise the programme should begin with low impact exercises e.g., step aerobics and intermittent jogging [C].*
- *As fitness and muscle strength improve, the impact aspect of the programme must be progressed in intensity. A well designed and safe programme will include both high and low impact activities [C].)*
- *Specific attention should be paid to those with pelvic floor and joint conditions [C].*

Exercise in adults with osteoporosis

The conclusions of studies reporting that exercise regimens improve bone health in postmenopausal women have inferred that such programmes may be beneficial to those who suffer with osteoporosis. Kerr showed that postmenopausal BMD was significantly improved by a 12 month site specific strength training regimen of high load/low repetitions but not by an endurance regimen of low load/high repetitions (Kerr et al, 1996). Aerobic and strength exercises help to slow bone loss (Kelley et al, 1998).

Recommendations

- *High load, low repetitions programme: target sites would include muscle groups around the hip, wrist and spine [C].*
- *Weight bearing activities should be targeted preferentially to osteoporotic sites [C].*
- *If lung function allows aerobic and strength exercises should be considered with appropriate progression over time [C].*

Exercise for adults with a history of fracture

Exercise regimens should be altered for this group.

Recommendations

- *Low impact, low intensity activities e.g., walking, stair climbing, strength training initially with short levers or body resistance. All exercise programmes should be progressive [C].*

8. TABLES

**Table 8.1 Vitamin D preparations containing only vitamin D.
(See calcium table for preparations containing calcium with vitamin D)**

| | |
|--|---|
| Alfacalcidol (hydroxylated vitamin D, 1 α - hydroxycoleciferol, 1 α -hydroxyvitamin D ₃) | 250 & 500 nanograms capsules, 1 microgram capsule |
| | Oral drops 2 micrograms/ml (one drop contains approx. 100 nanograms) |
| Calcitriol (1, 25 dihydroxycoleciferol, 1, 25dihydroxyvitamin D ₃) | 250 & 500 nanograms capsules |
| Ergocalciferol tablets (calciferol, vitamin D ₂) | 250 micrograms (10,000 units) |
| | 1.25 milligrams (50,000 units) |

**Table 8.2 Multivitamin preparations containing vitamin D
(without calcium)**

| | Vitamin D IU (International units) (as ergocalciferol) | Vitamin A (IU) | Vitamin E (IU) |
|--|---|-----------------------|-----------------------|
| A&D capsules | 400 (10 micrograms) | 4000 | |
| Abidec [®] (0.6 ml) | 400 (10 micrograms) | 1333 | |
| Dalivit [®] (0.6 ml) | 400 (10 micrograms) | 5000 | |
| Multivitamins BPC | 300 (7.5 micrograms) | 2500 | |
| Ketovite [®] liquid (5 ml) | 400 (10 micrograms) | 2500 | |
| ADEK [®] tablets | 400 (10 micrograms) | 4000 | 100 |

Table 8.3 Vitamin D synonyms

| Recommended International Non-proprietary Name (rINN) | Other names |
|--|---|
| Alfacalcidol | 1 α -hydroxycoleciferol; 1 α -hydroxyvitamin D ₃ ; 1 α -OHD ₃ |
| Calcifediol | Calcidiol, 25-hydroxycoleciferol; 25-hydroxyvitamin D ₃ ; 25-(OH)D ₃ |
| Calcitriol | Calcitriolum; 1,25- dihydroxycoleciferol; 1 α ,25- dihydroxycoleciferol; 1 α ,25-dihydroxyvitamin D ₃ ; 1 α ,25(OH) ₂ D ₃ |
| Colecalciferol | Activated 7-Dehydrocholesterol; coleciferol; coleciferolum, Vitamin D ₃ |
| Doxercalciferol | 1 α -hydroxyergocalciferol; 1 α -hydroxyvitamin D ₂ ; 1 α -OH-D ₂ |
| Ergocalciferol | Calciferol; ergocalciferolum; Vitamin D ₂ |

Table 8.4 Vitamin D and calcium content of commonly used supplements.

| Preparation | Vitamin D IU (micrograms) | Calcium mg (mmol) | Comment |
|--|--------------------------------------|------------------------------|--|
| Adcal-D ₃ Forte®(coleciferol) | 400 (10) | 600 (15.1) | Can be dissolved in water |
| Calcit D ₃ ®sachets (coleciferol) | 400 (11) | 500 (12.6) | Mix with water |
| Calceos® (coleciferol) | 400 (10) | 500 (12.6) | Chewed or broken and swallowed |
| Calcium and ergocalciferol | 400 (10) | 97 (2.4) | Alpharma brand contains no animal products |
| Calcichew D ₃ ® (coleciferol) | 200 (5) | 500 (12.6) | Chewed or broken and swallowed |
| Calcichew D ₃ Forte® (coleciferol) | 400 (10) | 500 (12.6) | Chewed or broken and swallowed |
| Calfovit D ₃ ® (coleciferol) | 800 (20) | 1200 (30) | Mix with water |

Table 8.5 Calcium supplements

| Preparation | Calcium mg (mmol) |
|--|--------------------------|
| Calcium Gluconate tablets | 53.4 (1.35) |
| Calcium Gluconate effervescent tablets | 89 (2.25) |
| Calcium Lactate tablets | 39 (1) |
| Adcal® (carbonate) | 600 (15) |
| Cacit® (carbonate) | 500 (12.6) |
| Calcichew® (carbonate) | 500 (12.6) |
| Calcichew Forte® (carbonate) | 1000 (25) |
| Calcium 500® syrup (5 ml) | 108.3 (2.7) |
| Calcium-Sandoz® Syrup (5 ml) | 108.3 (2.7) |
| Sandocal -400® tablets (mixed) | 400 (10) |
| Sandocal -1000® tablets (mixed) | 1000 (25) |

9. GLOSSARY

| | |
|-------------------------|---|
| aBMD | Areal bone mineral density |
| BMC | Bone mineral content |
| BMD | Bone mineral density |
| BMI | Body mass index (kg/m ²) |
| CFRD | Cystic fibrosis-related diabetes |
| CFRLD | Cystic fibrosis-related liver disease |
| CFTR | Cystic fibrosis transmembrane conductance regulator |
| CRP | C-reactive protein |
| DXA scan | Dual energy x-ray absorptiometry scan |
| FEV ₁ % | Forced expiratory volume in one second, percent predicted |
| IL-1 | Interleukin 1 |
| IL-6 | Interleukin 6 |
| IVA | Immediate visual assessment |
| OPG | Osteoprotegerin |
| pBMCV | Peak bone mineral content velocity |
| PCA | Patient controlled analgesia |
| PTH | Parathyroid hormone |
| QCT | Quantitative computed tomography |
| QUS | Quantitative ultrasound |
| RANKL | Receptor activator of NF Kappa B ligand |
| TENS | Trans-cutaneous electrical neural stimulation |
| TNF alpha | Tumour necrosis factor alpha |
| WHO | World Health Organisation |
| 25OHD | 25 hydroxyvitamin D |
| 1,25(OH) ₂ D | 1,25 dihydroxyvitamin D |

Notes



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ISBN 0-9548511-0-2