

CF Guidelines - Osteoporosis

Management of Osteoporosis in CF:

The true prevalence of CF (cystic fibrosis) related bone disease is unknown as universal screening has not to date, been implemented. Reported prevalence rates for osteoporosis in adults with CF vary from 3.3% (The Cystic Fibrosis Foundation 2000 Patient Registry Annual Data Report) – 39% (elkin et al 2001) and for osteoporosis from 2.6% (The Cystic Fibrosis Foundation 2000 Patient Registry Annual Data Report) – 57% (elkin et al, 2001). The variability in reported rates being dependent on the level of screening and the risk status of the population screened. Reported prevalence of reduced bone mineral density (BMD) in CF children and adolescents vary from 0.2% (The Cystic Fibrosis Foundation 2000 Patient Registry Annual Data Report) - 87%. (Henderson et al 1999) Puberty is the time of greatest bone mineral deposition. Delayed puberty is common in cystic fibrosis and may contribute to low BMC (bone mineral content) and reduced peak BMD seen in adolescents and young adults. (Flohr F et al). Well children with CF have bone mineral density similar to non CF controls (Buntain et al 2004, Hardin et al 2001, Sood et al 2001) suggesting that well children with CF have smaller but normally mineralised bones. Risk factors known to be associated with osteoporosis in CF include nutritional status, cortico-steroid usage, delayed puberty and disease severity. (Bhudhikanok et al 1996) Increased bone loss in adulthood may contribute to low BMD. Abnormal bone turnover with decreased osteoblastic and increased osteoclastic activity are seen in CF patients. Vitamin D deficiency is commonly reported in CF but may (Hahn et a 1979) or may not be associated with reduced BMD.

Vitamin K deficiency may influence osteocalcin carboxylation. Poor nutrition and low BMI (body mass index) commonly seen in CF are associated with low BMD. Lung infection and inflammation are associated with an increase in inflammatory cytokines IL6, IL1 and TNFa which increase osteoclastic activity and biochemical markers of bone resorption. (Aris et al 2000, Ionescu et al 2000). Sex hormone and insulin deficiency in CF are also likely to contribute to low BMD. Oral and inhaled cortico steroids and the use of Depo Provera may also contribute to bone loss. (Yen et al 2002) The consequences of osteoporosis include new rib and vertebral fractures which can interfere with pulmonary function and chest physiotherapy. As for osteoporosis there is no universal routine screening for detecting fractures in patients with cystic fibrosis. Reported fracture incidence rates vary from 0.4% (The Cystic Fibrosis Foundation 2000 Patient Registry Annual Data Report) - 50% (Aris et al 1998) of adult CF patients. Many of these fractures are not reported at the time of occurrence. (Elkin et al 2001).

Prevention of Osteoporosis in CF:

- Nutrition:
 - Regular and frequent dietetic review.
 - Maintain weight at > 90% predicted for height or BMI at > 25% predicted.
 - Monitor calcium intake (1,300-1,500 mg/day if >8 years of age).
 - Calcium supplements to be taken at different time of day to bisphosphonates, ciprofloxacin and iron.
 - Consider Vitamin K supplementation of 300 micrograms/kg/day age <2yrs, 5 mg/day (phytomenadione), age 2-7 years, 10 mg/day age >7yrs.
 - Measure Vitamin D (25OHD) levels at diagnosis, annually and after dose adjustment, supplementation of 400 iu/day (age < 1 year), 800 iu/day

(age > 1–12 years), 800 -2000iu/day (age >12 years) Maintain serum 25OH levels between 30 and 60 ng/ml (70-100 nmol/L).

- Increase Vitamin D supplementation if circulating 25 (OH)D levels <30 mcg/ml Winter/Spring.
- If 25OH levels are below 10 ng/ml (25nmol/L) or the corrected serum calcium is low, measure PTH.
- If 25OH levels do not respond adequately to increased doses of oral ergocalciferol e.g. in advanced liver disease, UVB therapy or Vit D analogue such as Calcitriol or Alfacalcidol should be used at annual screening monitor Mg, Zn and Cu intake to achieve RDA.

- Exercise:
 - Encourage physical activity and regular weight bearing exercise.

- Inflammation:
 - Optimise treatment of lung infection.

- Alcohol and Tobacco:
 - Avoid tobacco and minimise alcohol intake.

- Endocrine:
 - Monitor bone age in children whose height velocity is reduced or whose height centile is less than that predicted from their mid-parental height. Screen annually for glucose intolerance secondary to insulin deficiency in patients of > 12 years of age.

Screening for Osteoporosis:

Screen annually for puberty in females > 9 years and males > 11 years, until they have completed puberty. Assess menstrual history regularity and for early menopause annually. Measure serum testosterone levels on an annual basis in adult males. Consider endocrine referral and hormone replacement therapy for pubertal delay and hypogonadism. Try to avoid the use of medroxyprogesterone and other progesterone – only preparations as they may lower BMD. Monitor steroid usage and reduce dose if possible.

Monitor chest X-rays for evidence of fractures and bone loss annually. Baseline DEXA scanning of lumbar spine (and proximal femur in adults and children if available) in all CF patients aged >10 years of age, this is especially important in patients:

- With delayed puberty or amenorrhoea.
- With failure to thrive (weight < 90% predicted for height) or BMI < 25% predicted.
- With moderate/severe lung disease (Lung function < 70% predicted).
- Post organ transplantation.
- Who use high dose systemic cortico-steroids > 90 days per year.
- Of > 18 years of age if not performed previously.
- Who have had low energy fracture.

Repeat DEXA scan - using the same machine, scanning mode, software and analysis if appropriate:

- Every 3 years if Z score -1.0 or above.
- Every 2 years if Z score -1 to -2.
- Annually if Z score -2 or below until stable or improved.
- Annually if on regular oral Prednisolone or on organ transplantation

waiting list or post transplantation or if documented bone loss from previous studies.

Decisions about timing of DEXA scan should be made at annual review. DEXA scans should be reported using Z scores in children, pre-menopausal women or men <50 yrs of age and in children interpreted in the light of the best available paediatric reference data (cited in the report). Adjustments to Z scores may need to be made in individuals of small body size. The diagnosis of osteoporosis should not be made in children on the basis of densitometric criteria alone. The term low mineral density for chronological age should be used in children if Z score is below -2 with the caveat that unadjusted Z scores may be unreliable in individuals of small body size.

Treatment:

General recommendations for treatment:

- Ensure calcium intake is appropriate for age.
- Ensure Vitamin D intake is adequate and that seasonal adjusted Vitamin D levels are satisfactory.
- Minimise use of oral cortico-steroid agents.
- Improve nutritional status.
- Encourage regular weight bearing exercise.
- Minimise pulmonary infection/inflammation.
- Administer hormone replacement therapy for delayed puberty or Hypogonadism.

Use of Bisphosphates:

Bisphosphonates inhibit osteoclastic bone resorption. Bone turnover studies in CF patients demonstrate an imbalance of bone resorption and formation, however, the use of bisphosphonates may be problematic in CF because:

- There is a high incidence of concurrent Vitamin D deficiency.
- Poor gastro-intestinal absorption of bisphosphonates seen in the general population (0.75% of dose taken) may be even worse in CF patients.
- Oral aminobisphosphonates can cause erosive oesophagitis which may be of increased severity in the CF population who already have a high prevalence of gastro-oesophageal reflux.
- Bisphosphonates have been largely evaluated in post menopausal women and there is continued uncertainty as to their potential long-term effects on skeletal development and teratogenicity. Their use has associated with osteonecrosis of the jaw.

Studies have demonstrated a significant improvement in bone density in the adult CF population after treatment with intravenous pamidronate and oral alendronic acid. A six month trial in non-transplant patients has demonstrated a 5.8% difference in lumbar spine bone density and 3% difference in total hip density between the pamidronate and control groups.(Aris et al 2000). However, there was a high incidence of bone pain in patients not taking oral cortico-steroids. A two year trial in post-transplant CF adults has demonstrated an 8.8% increase in bone density in the lumbar spine and 8.2% increase in bone density in the proximal femur compared to the CF control population who gained 2.6% and 0.3% respectively.(12 A 12 month randomised double blind controlled study of alendronic acid in 48 adults with CF with low bone density (Aris et al 2004) showed a mean +/- SD in BMD of $4.9\pm 3.0\%$ 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 ($p<0.003$).

Bisphosphate therapy should be considered in adults if:

- Patients with a lumbar spine or femoral neck or total hip Z-score of <-2 who have significant bone loss ($>4\%$ per year) on serial DXA scans despite implementation of the general measures described above.
- CF patients with a previous osteoporosis related fracture or low energy fracture.
- CF patients requiring long-term (>3 months) of oral corticosteroid therapy with a lumbar spine or femoral neck or total hip Z-score of <-1.5 .
- CF patients listed for or following organ transplantation who have with a lumbar spine or femoral neck or total hip Z-score of <-1.5 .

Bisphosphate therapy may be considered in children if:

- Patients with a lumbar spine or femoral neck or total hip Z-score of <-2 who have significant bone loss ($>4\%$ per year) on serial DXA scans despite implementation of the general measures described above.
- Patients listed for or post organ transplantation who have had a low energy fracture.

A decision to start Bisphosphate therapy should only be made by a CF Consultant. Discussion with a Metabolic Bone Disease Specialist (e.g. Christine Burren @ UBHT Bristol).

Choice of Bisphosphonate Therapy:

- Choice should be governed by clinical circumstance and patient preference, patient adherence, coexistent upper GIT pathology etc.
- Suitable choices would include oral Risedronate (5mg OD) or 30mg weekly which has shorter shelf life, and better tolerability or oral Alendronate 70mg weekly.

In order to reduce the risk of bone pain administer at the end of an intravenous antibiotic course. If bone pain develops as a consequence of bisphosphonate therapy then ibuprofen or paracetamol should be used. If analgesics are ineffective a 3 day course of oral Prednisolone (20-30 mg daily) starting on the day before Pamidronate infusion could be trialed.

Considerations when using Bisphosphonate Therapy:

- Female patients need to use adequate contraception and be counselled about the postnatal risk of foetal tetragenicity.
- Informed consent should be documented in medical notes.
- Bisphosphonate therapy should not be prescribed in osteomalacia if the serum 25OHD is $<10\text{ng/ml}$ and the PTH and/or calcium level is increased refer patient to a bone specialist.
- Bisphosphonate therapy should not be prescribed in severe renal impairment (creatinine clearance $< 30\text{ml/min}$).
- Renal function, serum corrected calcium, potassium and magnesium levels should be monitored.
- Oral bisphosphonate therapy should not be prescribed in patients with oesophageal varices.
- DXA should be repeated 6-12 months after starting treatment and oral therapy should be switched to intravenous bisphosphonate therapy if BMD has decreased significantly.

Administration of Bisphosphonates:

- At the end of an intravenous antibiotic course.
- After commencing a 3 day course of oral Prednisolone (20-30 mg daily) two days before pamidronate infusion if patient suffers from significant bone pain. Paracetamol or ibuprofen may also be prescribed.
- Separately to calcium supplements if using an oral bisphosphonate preparation.
- Weekly oral regimens are likely to be preferable to daily regimens.

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