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European cystic fibrosis bone mineralisation guidelines

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Abstract

Patients with cystic fibrosis (CF) are at risk of developing low bone mineral density (BMD) and fragility fractures. This paper presents consensus statements that summarise current knowledge of the epidemiology and pathophysiology of CF-related skeletal deficits and provides guidance on its assessment, prevention and treatment. The statements were validated using a modified Delphi methodology.

Keywords: Cystic fibrosis; Dual Energy X-ray Absorptiometry (DXA); Bone density; Fractures; Bisphosphonates; Calcium; Vitamin D; Puberty

1. Introduction

It is now widely recognised that people with cystic fibrosis (CF) are at increased risk of developing low bone mineral density (BMD) and sustaining a low trauma fracture. The purpose of this EuroCareCF-funded work package was to develop consensus statements that (a) summarise current knowledge of the epidemiology and pathophysiology of CF-related low BMD and (b) provide guidance on its assessment, prevention and treatment.

2. Methods

A list of topics was defined by a core group and a comprehensive search undertaken for published and unpublished literature on these topics by a working group of clinicians with a research interest in CF bone disorders from Europe and North America. After completing this process, statements were drafted by the working group at a meeting in Paris in June 2009 and graded according to the recommendations of the Scottish Intercollegiate Guidelines Network [1].

Statements were grouped into general and specific risk factors for CF bone disease, assessment of bone health, prevention strategies for CF bone disease and treatment strategies of CF bone disease. The statements for risk factors and preventive/curative treatments were further divided into nutrition, endocrine issues, calcium, vitamin D and vitamin K therapies. Monitoring of glucocorticoids, indications for and monitoring of bisphosphonate treatment were also considered.

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European experts, selected according to their interest in both CF and bone metabolism, were invited to participate in the validation of the statements using a modified Delphi methodology [2]. Participants were sent the list of statements and asked whether they agreed, disagreed or were unable to comment on each. If they disagreed they were asked to provide a reason and an alternative statement. References were also requested, in case trials had been overlooked in the initial search strategy. The Delphi process was overseen by two facilitators (I. Sermet-Gaudelus and C.S. Haworth) whom sought further advice from experts on comments that arose during the Delphi process. We determined that 80% agreement would determine an adequate consensus on a statement [3]. However, even if consensus was achieved, comments were still considered and incorporated if it was felt by the facilitators that they significantly improved or clarified a statement.

3. Results

3.1. Literature review

The quantity and quality of published trials on CF bone disease was considered poor. Most interventions were graded as D (evidence from published case reports/series or expert opinion). Statements were derived from experience in managing patients with other bone diseases, especially postmenopausal osteoporosis, but also from many forms of secondary osteoporosis, including in children. This was particularly necessary for the statements relating to bone mineralisation assessment with bone densitometry.

3.2. The modified Delphi process

The core group developed 82 statements, which were used in Round One of the modified Delphi process. Thirty CF specialists from Europe contributed to the modified Delphi process. Consensus was not achieved for 30 statements in Round 1 and these were subsequently modified by the facilitators taking into account comments and suggestions from the European CF specialists and the working group (five statements were deleted, 25 statements were modified (two of which were also merged). Eight statements were adjusted, despite achieving consensus, as the facilitators considered that this improved the quality of the statements. In Round 2 a consensus was achieved for all statements (Table 1).

4. Discussion

The most controversial statements in Round 1 related to (1) optimal vitamin D concentrations and supplementation regimens; (2) the interpretation of bone densitometry data, particularly in children and adolescents; and (3) the use of bisphosphonates in children and adolescents.

4.1. Optimal vitamin D concentrations and supplementation regimens

Serum 25-hydroxyvitamin D is the best biochemical marker of vitamin D status, yet optimal lower and upper thresholds for desirable levels in the CF population are still a matter of debate. A threshold level of 20 ng/ml (50 nmol/l) to prevent vitamin D deficiency has been suggested in the current guidelines. A threshold of 20 ng/ml has also been recommended by the Lawson Wilkins Pediatric Endocrine Society based upon pediatric data available to date [4]. This contrasts with the North American CF bone health consensus statement which recommends achieving a minimum 25-hydroxyvitamin D concentration of 30ng/ml [5]. Higher 25-hydroxyvitamin D concentrations may offer extra skeletal health benefits including enhanced immune function and a reduced risk of developing diabetes, cancer and cardiovascular disease [6]. However, no consensus has yet been reached regarding the serum concentration of 25-hydroxyvitamin D required to optimise bone mineralisation in children, adolescents and young adults with or without CF. While it is clear that patients with CF require vitamin D supplements and have lower 25-hydroxyvitamin D levels and higher parathyroid hormone (PTH) levels than healthy controls, cross-sectional studies show no clear association between BMD and the vitamin D status of patients with CF [7]. In addition, the 2 interventional studies so far performed show no effect on bone mineralization and bone turnover markers [8,9]. Therefore, current data show no evidence to demonstrate a beneficial effect of levels above 30 ng/ml (75 nmol/l) on bone mineral density, fractures and markers of bone metabolism in people with CF.

The 30 ng/ml cut-off proposed by Holick and colleagues is designed to keep PTH levels as low as possible [10]. This makes sense in elderly and adults as demineralisation may result from increased bone resorption induced by elevated PTH levels. This concept may not be valid in all situations, as already demonstrated in patients with chronic renal insufficiency where too low PTH levels block bone formation and induce the so called "adynamic bone disease". Along this line, too low PTH levels may be detrimental in children and young adults as it has been suggested that PTH levels in the high normal range may favour bone formation [11]. Moreover, the long term consequences of maintaining 25-hydroxyvitamin D levels above 30ng/ml have not been extensively explored in large groups of children or young adults.

Studies are also lacking to determine the most effective vitamin D supplementation regimen to correct vitamin D deficiency in people with CF [12]. However, recent data suggest that 50,000 IU vitamin D3 (cholecalciferol) weekly for 3 months may be a successful means of increasing 25-hydroxyvitamin D levels [13]. This study also suggests that supplementation with vitamin D3 may achieve higher levels of 25-hydroxyvitamin D than supplementation with vitamin D2, a finding that has also been reported in the general population [14]. However, potential failure of such supplementation modality in patients with CF requires that in

Table 1

Description and Pathophysiology of Bone Disease in CF

General Statements

1. Bone mineral content (BMC) and bone mineral density (BMD) are usually normal in children who have normal nutritional status and well preserved lung function. However, several cross-sectional studies have found low BMC/BMD in children, possibly because of low bone mass accrual. Further longitudinal studies are needed to confirm these observations.
2. Reduced BMD is common in adolescents and adults. Longitudinal studies suggest lower peak bone mass accrual in adolescence, following which bone loss may occur prematurely.
3. Adults have an increased risk of fracture compared to a healthy population of the same age and gender.
4. Transplant listed patients and transplant recipients usually have low BMD and are at risk of low trauma fracture.
5. In CF, low BMD results from an imbalance in bone remodeling with decreased bone formation and increased bone resorption, especially during infective exacerbations.
6. Potential risk factors for CF bone disease include: poor nutritional status, lung infection, vitamin D insufficiency, vitamin K insufficiency, a negative calcium balance, abnormal fatty acid status, hypogonadism, delayed puberty, CF related diabetes, glucocorticoid treatment, reduced levels of weight bearing activity and the effect of CFTR dysfunction on bone cells.

Specific Risk Factors for CF Bone Disease

Nutritional status

7. There is a positive correlation between nutritional status and BMD.
8. Reduced lean body mass may contribute to reduced BMD.

Vitamin D

9. Vitamin D deficiency and insufficiency may result in impaired bone mineralisation and increased bone loss.

Vitamin K

10. Vitamin K deficiency may contribute to an alteration of the normal balance between bone formation and bone resorption. However, there is no evidence of a direct link between vitamin K levels and BMD.

Calcium

11. Some studies suggest that people with CF are at increased risk of negative calcium balance that may adversely affect bone health.

Infection/systemic inflammation

12. Lung infection adversely affects bone health. There is an inverse relationship between BMD and the number of antibiotic courses, levels of serum C reactive protein and serum interleukin 6.

Endocrine issues

13. Puberty is a key time for bone development. Peak growth velocity is associated with high bone mass accrual. Pubertal delay is common in children with CF and may result in suboptimal bone acquisition.

Glucocorticoids

14. Continuous systemic glucocorticoid therapy is a significant risk factor for bone loss and fracture, as it is in the general population. The effect increases with daily dose and cumulative dose.

Assessment of Bone Health in CF

Dual Energy X-ray Absorptiometry Evaluation

15. Dual energy X-ray absorptiometry (DXA) is currently the gold standard method for measuring bone mineral content (BMC) and bone mineral density (BMD) in people with CF.
16. DXA scans should be performed in centres experienced in interpreting BMD data from people with CF. Normative data should be age, gender and geographically matched to the patients measured.
17. BMD should be measured at the total body and the lumbar spine in patients younger than 20 years of age, and at the lumbar spine and proximal hip in patients of 20 years of age or older.
18. BMD values should be expressed as Z-scores* in premenopausal women and men under 50 years of age, and as T-scores in postmenopausal women and in men 50 years of age or older. If Z-scores are not available, T-scores can be used in CF patients above 20 years of age. Until the age of 20, only the Z-score can be used.
19. With DXA, BMD deficits may be overestimated in patients with short stature, because they display a more severe decrease in bone area than in bone mineral content.
20. For patients younger than 20 years of age whose height is at least 1 SD below age and sex matched healthy controls, BMD Z-scores should be adjusted for height or statural age to avoid overestimating deficits in BMD in people with short stature.
21. The term "CF related low BMD" may be applied to children and adults with a BMD Z-score below -2.
22. In CF children, adolescents or young adults up to the age of 20 years, osteoporosis is defined as having a BMD Z score < -2 and a significant fracture history (low trauma fracture of a lower limb long bone, vertebral compression fracture, or two or more upper limb long bone fractures).
23. In postmenopausal women or men over the age of 50 years with CF, osteoporosis is defined as having a BMD T-score ≤ -2.5. In younger adults, osteoporosis is defined as having a BMD Z score < -2 and a significant fracture history. The term osteoporosis can also be applied to adults with CF who have sustained a low trauma fracture as it is an indicator of increased bone fragility.
24. In children, routine bone density scans should first be performed from around the age of eight to 10 years, and should be repeated approximately: every five years if the BMD Z-score is > -1; every two years if the Z-score is between -1 and -2; and every year if the Z-score is < -2 or if the child has experienced low trauma fractures. Bone density measurements can be first done at an earlier age and/or yearly in children with significant risk factors for low BMD and in children before prescribing specific treatments for low BMD.

* The Z-score is the difference (expressed as the number of Standard Deviations) between a patient's bone mineral density value and the average value of an age- and gender-matched healthy population. The T-score is the difference (expressed as the number of SD) between a patient's bone mineral density and the average value of a population of healthy young adults of the same sex.

Table 1 (continued)

25. In adults with CF less than 50 years of age, routine bone density scans are recommended approximately: every five years if the BMD Z-score is > -1; every two years if the Z-score is between -1 and -2; every year if the Z-score is < -2. BMD measurements can be done yearly in adults with significant risk factors for low BMD. BMD measurements must be done before prescribing bone protective therapy.
26. In adults after 50 years of age, routine bone density scans are recommended approximately: every five years if the T-score is > -1; every two years if the T-score is between -1 and -2.5; every year if the T-score is < -2.5. BMD measurements can be done yearly in adults with significant risk factors for low BMD. BMD measurements must be done before prescribing bone protective therapy.
27. Fracture history should be included in the medical record.
28. Vertebral fractures are often under-diagnosed. Chest X-rays should be routinely examined for the presence of vertebral fractures.
29. Vertebral fracture evaluation should be performed using lateral thoracolumbar spine X-rays in patients with low BMD, height loss and/or back pain. Vertebral fracture diagnosis should be based on visual evaluation and the assessment of grade/severity of vertebral deformity. The Genant visual semi-quantitative method is the current clinical technique of choice for diagnosing vertebral fracture with X-ray and with DXA morphometry.

Nutrition

30. In children, height must be recorded at every clinic and in-patient hospital visit and plotted on the appropriate percentile chart.
31. In adults height must be recorded at every clinic and inpatient hospital visit until growth has ceased and annually thereafter.
32. In children and adults, weight must be recorded at every clinic and in-patient hospital visit. In adults, weight and height measurements should be converted to body mass index (kg/m^2). In children over 2 years, BMI measurements should be plotted on the appropriate percentile chart and expressed as either percentile positions or standard deviation scores.
33. There should be periodic assessment (at least annually) of dietary energy, protein and calcium intake by a dietitian experienced in the management of patients with CF. This should be assessed more frequently in case of abnormal growth velocity or weight loss.

Vitamin D

34. Assessment of vitamin D status should include as a minimum: serum 25-hydroxyvitamin D, serum calcium, serum phosphorus and parathyroid hormone concentrations. Optimally, urinary calcium excretion should be measured (either as the quantity of calcium in the total daily output (in mg/day) or as the ratio calcium/creatinine on a morning urine sample) in patients prescribed vitamin D supplements.
35. The assay used to measure 25-hydroxyvitamin D should measure both vitamin D2 and vitamin D3 as this is essential to accurately determine vitamin D status.
36. The 25-hydroxyvitamin D assay must adhere to internationally validated standards.
37. No consensus has yet been reached regarding the serum 25-hydroxyvitamin D concentration required to optimise bone mineralisation in children, adolescents and young adults, with or without CF. Moreover, the long term consequences of maintaining 25-hydroxyvitamin D levels above 30 ng/ml have not been extensively explored in large groups of children or young adults. To prevent vitamin D deficiency, we recommend a minimum 25-hydroxyvitamin D concentration of 20 ng/ml (50 nmol/l).

Calcium

38. There are no simple biochemical indicators of calcium status for use in clinical practice.
39. A specialist CF dietitian should assess calcium intake at least annually.

Vitamin K

40. Vitamin K status is best assessed by measuring serum concentrations of vitamin K_1, PIVKA-II and under-carboxylated osteocalcin. If these are not available, the prothrombin time can be measured, accepting that this is a less sensitive marker of vitamin K deficiency.

Endocrine assessment

41. Routine clinical visits should include accurate measure of both height and weight to calculate growth velocity in children. Height and weight must then be recorded on a growth curve and expressed as BMI percentile positions. Height velocity should also be analysed.
42. An evaluation of pubertal development should be performed at least twice a year in peripubertal children until pubertal development is complete.
43. Patients who do not have normal growth velocity or who fall two standard deviations below their target height should have a rigorous endocrine evaluation, which may include an assessment of the growth hormone–insulin-like growth factor-1 axis.

CF Bone Disease: Prevention Strategies

Recommendations for nutritional interventions

44. A normal body mass index with particular attention to lean body mass is important to optimize bone health.

Recommendations for control of lung infection/systemic inflammation

45. CF pulmonary exacerbations should be treated promptly to minimise adverse effects of systemic inflammation on bone.

Recommendations for vitamin D supplementation

46. All patients with vitamin D deficiency and insufficiency should be prescribed vitamin D supplements.
47. Studies are lacking to determine the most effective vitamin D supplementation regimen to correct vitamin D deficiency. In these circumstances, we recommend a starting dose of 1000–2000 IU/day of vitamin D_2 or D_3 in infants; and a starting dose of 1000 to 5000 IU/day of vitamin D_2 or D_3 in children above one year of age and in adults. The dose should then be adjusted aiming to maintain 25-hydroxyvitamin D concentration above the deficiency threshold of 20 ng/ml (50 nmol/l). Current evidence favours supplementation with vitamin D_3 over D_2.

Recommendations for calcium supplementation

48. To maximise skeletal accretion of calcium and optimise bone health in CF, daily calcium intakes should as a minimum achieve the levels recommended by the Food and Nutrition Board, for each age group, as following: 0–6 months: 210 mg; 7–12 months: 270 mg; 1–3 years: 500 mg; 4–8 years: 800 mg; 9–18 years: 1300 mg; 19–50 years: 1000 mg; >50 years: 1200 mg**.
49. Those with suboptimal calcium intakes should be advised to increase dietary sources of calcium. If necessary, calcium supplements can be given.

** Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. National Academy Press, Washington, D.C, 1997.

Table 1 (continued)

Recommendations for vitamin K supplementation

50. Vitamin K supplementation is recommended for all pancreatic insufficient patients.
51. Studies are lacking to determine the most effective vitamin K supplementation regimen to correct vitamin K deficiency. In these circumstances, we recommend a starting dose of at least 0.5 mg to 2 mg/day in infants with CF; and a starting dose of at least 1 to 10 mg/day in children above one year of age and adults with CF. Additional vitamin K_1 supplementation may be considered in patients with low vitamin K_1 levels, a prolonged PIVKA II, increased levels of under carboxylated osteocalcin or a prolonged prothrombin time.

Recommendations for weight bearing exercise

52. Children and adolescents should be encouraged to exercise for 20–30 minutes three times a week in addition to their usual activities. Activities should include high impact weight bearing activities such as jumping or skipping. This is likely to be most beneficial in the prepubertal and early pubertal stages.
53. Adults should be encouraged to perform regular weight bearing and resistance activities. Exercise programmes should be individualised. For those not used to doing regular exercise, the programme should begin with low impact exercises such as jogging. As fitness and muscle strength improve, the impact aspect of the programme can be increased.
54. When admitted to hospital, patients should be encouraged to continue their usual exercise programme, where possible.

CF Bone Disease: Treatment Strategies

Recommendations for the management of patients on glucocorticoids

55. The use of oral glucocorticoids should be minimised whenever possible.
56. Bisphosphonate treatment should be considered for adults taking continuous systemic oral glucocorticoids for $\geq$ three months with a bone mineral density Z/T-score of -1.5 or less, and for adults who sustain a low trauma fracture while taking systemic glucocorticoids.
57. According to previous studies in non CF children, bisphosphonate treatment should be considered (in collaboration with a paediatric bone expert) for children taking continuous systemic glucocorticoids for $\geq$ three months and a history of low trauma fracture and/or bone mineral density Z-score of -2 or less.
58. Bone densitometry should be performed yearly in patients prescribed continuous systemic glucocorticoids.

Recommendations for endocrine interventions

59. If sex steroid deficiency is suspected, it should be assessed by total and free testosterone in males, and oestradiol and sex hormone binding globulin in females.
60. Sex steroid hormone replacement is recommended in adults with laboratory confirmed sex steroid deficiency.
61. Growth hormone treatment may be considered (in collaboration with an endocrine specialist) in children with severe growth delay. Before growth hormone treatment is initiated, malnutrition, malabsorption, CF-related diabetes and other causes of poor growth should be ruled out.

Recommendations for bisphosphonate treatment in adults

62. Bisphosphonate treatment should be considered in adults with CF when: a) the patient has had a low trauma fracture; and/or b) the lumbar spine or total hip or femoral neck Z/T-score is -2 or less and there is evidence of significant bone loss (>4% per year) on serial DXA measurements despite optimisation of their clinical care; and/or c) the patient is awaiting or has undergone solid organ transplantation and has a BMD Z/T-score of -1.5 or less; and/or d) the patient is starting a prolonged course of oral glucocorticoids (> three months) and has a BMD Z/T score of -1.5 or less.
63. Before prescribing bisphosphonates to adults with CF, vitamin D deficiency should be corrected and calcium intake must be optimised.
64. Calcium supplements should be prescribed if the patient's dietary intake is below the recommended intake or if the plasma calcium level is low. If the bisphosphonate preparation recommends calcium supplementation, this recommendation should be followed.
65. Patients should be counselled about the risk of osteonecrosis of the jaw and should consider seeing their dentist before starting bisphosphonate treatment if they have significant dental disease.
66. Oral bisphosphonates should be avoided in patients with oesophageal disease (including severe reflux and varices) in view of the risk of oesophageal ulceration.
67. Oral and intravenous bisphosphonates should be used cautiously in patients with chronic renal insufficiency.
68. Female patients should be advised to take appropriate contraception and counselled about the risk of bisphosphonates to the unborn child before starting bisphosphonate therapy.
69. The prescription of paracetamol, or non steroidal anti-inflammatory drugs, or prednisone may be considered prior to first bisphosphonate infusion to reduce the incidence of bone pain and flu-like symptoms. Non steroidal anti-inflammatory drugs or paracetamol may also be prescribed prior to starting oral bisphosphonates to reduce the incidence of flu-like symptoms. These symptoms are mainly observed one to three days after the first dose of bisphosphonate therapy and are more common with intravenous than oral formulations.
70. Bone densitometry should be repeated after 12 months of bisphosphonate treatment to assess response and then repeated according to the algorithm in statements 25 and 26.

Recommendations for bisphosphonate treatment in children and adolescents

71. According to previous studies in non CF children, bisphosphonates treatment may be considered after failure of optimal conservative treatment for BMD in (a) children with CF with a BMD Z-score of -2 or less in the total body or lumbar spine and a history of low-trauma extremity fractures or vertebral compression fractures, and (b) in children with CF awaiting or who have undergone solid organ transplantation and have a BMD Z-score of -2 or less (c) in children with CF prescribed continuous systemic glucocorticoids and a bone mineral density Z-score of -2 or less (in collaboration with a paediatric bone expert).
72. Bone densitometry should be repeated after approximately 6 months of treatment to assess response and then repeated according to the algorithm in statement 24.

Recommendations for bisphosphonate treatment in transplant recipients

73. Low BMD and a history of low trauma fracture are not an absolute contraindication for lung transplant listing in people with CF.
74. Bone loss after solid organ transplantation can be lessened by the prescription of bisphosphonates in people with CF.

Recommendations for the management of rib and vertebral fractures

75. A chest X-ray should be performed to exclude pneumothorax in patients presenting with a suspected rib fracture.
76. Adequate analgesia is a priority for patients with painful rib or vertebral fractures to enable adequate chest expansion and airway clearance. If airway clearance is compromised, intravenous antibiotics and additional mucolytic therapies may be required.

all the cases, 25-hydroxyvitamin D levels should be measured after completing the supplementation courses [15,16].

4.2. Interpretation of bone densitometry data

In the last decade, the measurement of bone mineral content (BMC) and BMD in children and adolescents has become important in both research and clinical practice. The preferred technique for measuring BMD in younger subjects is dual-energy X-ray absorptiometry (DXA) because of its wide availability, low radiation dose and the ability to measure regional BMD (lumbar spine, proximal femur and forearm), as well as body composition. DXA also provides good measurement reproducibility or precision – the ability to reproduce the same numerical results in the setting of no real biological change when the test is repeatedly performed in an identical fashion [17]. In clinical practice, good reproducibility is dependent on the quality of the scanning procedure, which itself is dependent on the correct positioning of the patient, the protocol used for analysis and the systematic use of a calibration phantom. Precision can be further enhanced for longitudinal BMD measurements through using the same densitometer/ analysis software and the same operator as for the original measurement.

However, there are also significant technical challenges that need to be understood when interpreting DXA data, particularly from children and adolescents:

(1) DXA does not measure true bone mineral density (BMC/bone volume, g/cm^3), but only an "areal" bone density (BMC/bone projection area, g/cm^2). For mathematical reasons, the areal BMD is influenced by bone size, and tends to underestimate the true density value for smaller bones and to overestimate it for larger bones. Thus, the influence of body size must always be considered, not only for the initial assessment, but also in the follow-up of growing patients. Otherwise, an apparent increase in BMD may actually be an artefact due to an increase in bone size. A widely used correction of the vertebral "areal" BMD value obtained with DXA aims to approximate the volumetric density, based on the assumption that the vertebral body can be considered as a cylinder or a cube [18,19]. This correction of the "areal" density is called "bone mineral apparent density" (BMAD, g/cm^3). *In vivo*, the "volumetric" density can be more accurately measured by quantitative computed tomography. It should be noted that a definitive consensus on the best correction method has not been reached, but at a recent consensus conference the majority of experts agreed that "in children with linear growth or maturational delay, spine and total body less head BMC and areal BMD results should be adjusted for absolute height or height age, or compared to pediatric reference data that provide age-, gender-, and height-specific Z-scores" [20–22].

(2) DXA detects bone edges using a software algorithm and then the projected bone area is calculated. Edge detection algorithms designed for use in adults may not accurately detect the bone edges in children with low bone mineralization. Low-density software programs designed for use in children are available, but these results should be compared with those obtained with normative data also collected using low density software [23].

(3) The choice of an appropriate reference group is crucial for interpreting DXA data in children. The use of inappropriate reference data (for example data collected in children from a different ethnic group) can lead to errors in the calculation of Z-scores. Ideally, reference data used to evaluate BMD in growing patients should reflect not only the ethnicity, gender and age of the subjects being studied, but also body size and pubertal stage.

Finally, and above all, the clinical relevance of BMD evaluation is still not clearly defined in children [24]. In adults, BMD predicts the risk of osteoporotic fractures – the risk is estimated to double for each 1 SD decrease in BMD [25]. Recent data indicate that an association between bone density and fractures is found also in otherwise healthy children and that low BMD is associated with increased fracture risk in the subsequent two to five years [26–30]. Most studies [26–28,30] evaluated only forearm fractures because of their higher prevalence in children and adolescents. In a study on 6,213 children followed for 24 months, Clark et al. [29] found an association between bone density and all appendicular fractures. However, these data need to be confirmed by larger prospective studies. It must be clearly stated that the predictive value of low BMD for fractures remains uncertain in children, and pediatric bone experts agree that a diagnosis of "osteoporosis" cannot be made on the basis of BMD alone, but requires also the presence of a significant fracture history. According to the recent International Society for Clinical Densitometry (ISCD) Pediatric Position Development Conference, criteria for osteoporosis include low BMC or Areal BMD for age (Z-score < -2, after adjustment for age, gender and body size) and a clinically significant fracture history (one long bone fracture of the lower extremity, two long bone fractures of the upper extremity or a vertebral compression fracture) [22]. Regarding people with CF, the relationship between BMD and fracture risk has not been evaluated in cross sectional or longitudinal studies. Data from Canada suggest that BMD is a poor predictor of fracture risk in CF adults, indicating that bone quality may be an important determinant of fracture risk [31]. In children and adolescents with chronic diseases potentially affecting bone, like CF, repeated DXA scans require careful interpretation, taking into account both the physical changes occurring during growth (in particular, paying attention to any delay in growth or pubertal development) and the clinical changes induced by the primary disease. As a general rule, the repetition of a DXA scan should be considered every 1 to 2 years. In some cases a shorter time (6 months) could be considered, for example, if a change in the clinical status can be suspected of inducing a greater-than-expected change in bone density. To calculate the correct interval between scans, the least significant changes, based on the instrument's and technologist's precision, and the level of change that is considered clinically relevant must be taken into account [23].

Regarding the age for the first DXA scan in CF children (statement 24), the previously published U.S. guidelines

[5] recommended to perform it at 8 years. Some studies demonstrated that low BMD can occur even before this age. For example, among a cohort of 23 CF children below the age of 6 years, Sermet-Gaudelus et al. [32] reported that 13 patients had a BMD Z-score below −1.0 SD and 7 below −2.0 SD. Similar findings were reported by Bianchi [24]. Interestingly, in these studies low BMD was not related to the severity of CF disease based on lung function and nutritional parameters and low BMD was also found in patients with a moderate lung disease and normal nutritional status, suggesting that low BMD may be due to the intrinsic defect, i.e. CFTR dysfunction. Since most experts in the European working group found that bone loss is most often observed in the peripubertal age range (8-10 years) and fractures are infrequent in younger children, it was suggested that screening with DXA should usually commence at the age of 8 years.

4.3. Use of bisphosphonates in children and adolescents

Randomised controlled trials evaluating bisphosphonates in adults with CF suggest that both intravenous and oral formulations are effective in increasing BMD both in non-transplant and post transplant patients. However, none of the trials have been powered sufficiently to demonstrate an effect on fracture incidence.

The use of bisphosphonates in children with CF is more controversial because of potential long-term safety concerns including over suppression of bone remodelling [33]. However bisphosphonates are now regularly prescribed in children with osteogenesis imperfecta and in children with cerebral palsy related osteoporosis, in whom recurrent fractures affect quality of life and survival. Data also demonstrate the effectiveness of bisphosphonates in children with low BMD and fragility fractures associated with a variety of other disorders [34]. However, due to the difficulties in establishing the optimal dose/duration of therapy and in monitoring the therapeutic/the long-term effects of bisphosphonates, the prescription of bisphosphonates in children and adolescents should always be supervised by a paediatric bone specialist. Considering the reassuring short term (3 year) safety and efficacy data, bisphosphonate use is justified in CF children with reduced BMD associated with low-trauma extremity fractures and/or symptomatic vertebral compression fractures. They may also be indicated in children awaiting solid organ transplantation in anticipation of high dose steroid therapy [34].

5. Conclusion

This paper presents consensus statements developed through the EuroCareCF project that aim to harmonise clinical practice and improve bone health in children, adolescents and adults with CF. This process also highlights controversial issues such as vitamin D supplementation regimens and the use of bisphosphonates in children and adolescents indicating the urgent need for therapeutic trials in this area.

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Conflict of interest

None declared.

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