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The clinical features that contribute to poor bone health in young Australians living with cystic fibrosis: A recommendation for BMD screening

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Abbreviations:

ACFDR Australian Cystic Fibrosis Data Registry

ANOVA Analysis of Variance

BMD Bone mineral density

BMI Body mass index

CF Cystic fibrosis

CFTR Cystic Fibrosis Transmembrane Conductance Regulator

CFRDM Cystic fibrosis-related diabetes mellitus

CI Confidence interval

CLARA Clinical Lookup and Results Acknowledgement

CS Corticosteroid

DXA Dual energy x-ray absorptiometry

ESMR Electronic scanned medical record

FEV_1 Forced expiratory volume (litres) in 1 second

FVC Forced vital capacity

GLI Global Lungs Initiative

GT Glucose tolerance

LS Lumbar spine

MCRI Murdoch Children's Research Institute

OGTT Oral glucose tolerance test

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pQCT peripheral quantitative computed tomography

PTH Parathyroid hormone

RCH Royal Children's Hospital

SD Standard deviation

Abstract

Background: For Australians living with Cystic Fibrosis (CF), increased longevity means greater consideration needs to be given to long-term endocrine sequelae such as CF-related bone disease. Deficits in bone mass accrual most likely occur during childhood and adolescence. Current guidelines in Australia suggest repeat dual-energy x-ray absorptiometry (DXA) scans every 2 years. This study aims to stratify clinical factors that determine future bone health in the Australian CF population, and use this to guide a more streamlined approach to bone health screening.

Methods: This study was a retrospective audit of all patients diagnosed with CF who were treated at the Royal Children's Hospital Melbourne, Australia from 2000 to 2016 (n=453). 202 patients had a DXA scan in the study period (191 with height-adjusted data) and 111 patients had more than one scan (108 with height-adjusted data). An investigation into the associations between bone mineral density (BMD) Z score and potential risk factors was conducted using DXA and historical data.

Results: The main predictor of future BMD was previous BMD Z score ($p<0.001$). Other factors found to be determinants of BMD included nutritional status, lung function (FEV_1), age, history of previous fracture, oral corticosteroid use and number of hospital admissions. However, after adjusting for previous BMD, evidence of an association remained only with nutritional status, FEV_1 and number of hospital admissions.

Conclusion: Second yearly scans may be unnecessary in children with an adequate DXA score on initial scan who remain clinically stable. However, clinical deterioration in those

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whose bone mineral density were previously normal, may require closer monitoring of bone health. We propose a guideline for frequency of DXA monitoring in relation to clinical risk factors.

Introduction

Cystic fibrosis (CF) is the most common, life-shortening, autosomal recessive condition within the Caucasian population. In Australia, it has a prevalence of approximately 1 in 3000 newborns(1). Over the last 30 years, advancements in clinical care in CF have resulted in improved prognosis and people born with CF today have a mean predicted survival age of 46 years(1-3). As the availability of disease-modifying therapeutic options continues to improve, life-expectancy is also expected to increase, hence greater clinical care is now required for other long-term sequelae, including CF-related bone disease. CF patients often experience lower bone mineral density (BMD) compared to the healthy population, which carries an increased risk for fracture and vertebral deformity. These detrimental bone health outcomes have been well documented in adults, with the pooled prevalence of osteoporosis and osteopenia in adults with CF reported as 23.5% and 38.0% respectively, while vertebral and non-vertebral fractures were reported at 14.0% and 19.7%% respectively(4). It is thus crucial to screen for osteoporosis as CF-related bone disease has the potential to further compromise respiratory function, reduce physical activity and increase the health complications that these vulnerable patients already experience.

Several potential risk factors are believed to contribute to CF-related bone disease, which is likely to be a multifactorial process. These include malnutrition, corticosteroid use, pancreatic insufficiency, vitamin D and K deficiency, physical inactivity, delayed puberty and chronic inflammation (5). Genotype may also have a direct effect on bones, and individuals expressing the Phe508del mutation of the Cystic Fibrosis Transmembrane Conductance

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regulator (CFTR) gene may demonstrate lower BMD compared to those with other genetic mutations(6).

A recent systematic review and meta-analysis of BMD in CF patients compared to their healthy peers suggested that BMD development may not differ significantly but concluded that further longitudinal studies are required(7). This is a critical gap in knowledge, as CF-related bone disease most likely originates during the bone mass accrual process within the first 2 decades of life, where 90% of peak bone mass is reached (8).

Current research regarding the assessment of bone health in children is mainly derived from consensus-based guidelines, with little evidence to support CF specific recommendations. The Thoracic Society of Australia and New Zealand suggests proactive screening of BMD from 8 years of age, with repeat testing to be conducted at a minimum of every two years(9). The CF Foundation (United States) suggests children with CF undergo an initial DXA assessment at age 8 or older if they have significant risk factors for bone disease, with an algorithm for repeat testing determined by previous BMD Z score (10). In contrast, the European CF Society recommend routine scans to be initially performed in all children aged 8 to 10, regardless of their risk factors for bone disease, but also have an algorithm for repeat scans based on the initial results (11). The immediately pre-pubertal age range of 8-10 has been determined as the recommended commencement of screening since there is inadequate bone mass accrual at this time. The European group acknowledged that the quantity and quality of published trials on CF-related bone disease is poor and derived mostly from case reports and expert opinion only. Given the variance in current guidelines, a study that investigates the risk factors that contribute to poorer bone health and is able to provide a recommendation for the optimal screening of bone disease in CF patients would be of significant benefit.

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Our group has previously determined the prevalence of bone disease within a large unbiased population of Australian children and adolescents with CF and described the impact of lung function and body composition on bone health (12). However, this only looked at cross sectional data, and association with lung function, BMI and genotype. For this study following, the further aims were to identify and stratify the risk factors for bone disease by comparing BMD measured by DXA with a wide variety of clinical measurements, to explore the longitudinal drivers of changes of BMD in this population. Our objective was to use these risk factors and markers for disease severity to optimise screening guidelines and reduce the amount of unnecessary scanning in patients with perceived low risk for bone disease given their clinical profiles. In a cohort that already experiences the large burden of managing a chronic life-limiting disease, this would be greatly beneficial. Based on the findings, a proposed guideline for bone health screening is outlined.

Method:

Study design and participants

A retrospective audit was conducted on all patients (aged 4-19) who had been diagnosed with CF and were treated at the Royal Children's Hospital (RCH) Melbourne, Australia. A diagnosis of CF was confirmed by sweat test and/or genotype. Participants were included in the study if they had more than one DXA scan performed at the hospital between March 2000 and January 2016 and a height-adjusted Z score could be calculated.

Bone densitometry measurement

Bone mineral density at the lumbar spine (L2-4) (LS) and body composition were measured by dual energy x-ray absorptiometry (DXA) using either the Hologic QDR 4500 (pre-March 2015) or Horizon (post-March 2015) DXA scanner (Hologic Inc., Bedford, MA, USA) at the RCH. BMD was expressed as both a raw and a height-adjusted Z score (HAZ), a more reliable measure in paediatrics. BMD Z scores adjusted for height (using height Z score) were

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calculated using the BMDCS reference data(13). Lumbar spine was used as a more reliable measure compared to whole body BMD(14).

Anthropometric measurements

Weight and height were measured at the time of the DXA scan. Weight, height and BMI Z scores were calculated using the 2000 CDC Growth Reference Charts (15).

Respiratory function and clinical status

Spirometry results, specifically FEV_1,were used to measure lung function. The most recent data within 3 months of the DXA scan were collected from the Respiratory Medicine Department clinical database. Z scores for FEV_1 were calculated using the Global Lung-function Initiative (GLI) reference equations (16).

Genotype and pancreatic insufficiency status were ascertained using data provided by the Australian Cystic Fibrosis Data Registry (ACFDR). Participant genotype was grouped as Phe508del homozygous, compound heterozygous, or 'other' if they expressed 2 non-Phe508del mutations. Pancreatic status was based on use of current pancreatic enzyme replacement therapy, and was recorded as either 'sufficient' or 'insufficient' for all participants. CFTR (cystic fibrosis transmembrane conductance regulator) modulators were only introduced in December 2012 for a small subset of the patients, so most of the data preceded this.

Biochemical testing and historical data

Past medial history and clinical status for the patients was accessed through hospital records including corticosteroid use, biochemistry, radiology reports (for fracture history), sputum samples and oral glucose tolerance tests. Oral corticosteroid use was deemed significant if the patient received at least one month of high dose steroids (0.5mg/kg prednisolone equivalent or higher). Only data up to 12-months prior to the date of the DXA scan were recorded. In instances where multiple results were eligible, the result closest to the DXA scan was used.

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Ethics approval

The study was approved by The Royal Children's Hospital Human Research Ethics Committee; HREC #35056.

Statistical analysis

Mean and standard deviation (SD) are presented for all continuous data, as they followed a normal distribution. Linear regressions for BMD HAZ score were performed, examining one demographic and clinical measure at a time, and repeated adjusting for previous BMD Z score. Regression coefficients, 95% confidence intervals (CIs) and two-sided p-values are presented. Due to repeated measures from the same patient, standard errors allowing for clustering effects were calculated using the robust "information sandwich" method.

Analysis was performed using Stata version 16.1 (StataCorp, College Station, TX, USA, 2020).

Results

Patient demographics

Across almost 16 years of data collected at the RCH from 2000 to 2016, 453 patients were diagnosed with CF, of which 202 (45%) had at least one DXA scans and 111 (25%) had two or more. BMD HAZ scores were able to be calculated for only 191 patients. 108 of these patients had more than one DXA scan with a total of 307 DXA scans performed. The distribution is shown in Table 1.

The mean (SD) age at their initial DXA scan was 12.6 (2.2) years (Table 2). Patients demonstrated diminished lung function at baseline, with a mean (SD) FEV_1 Z score of -2.12 (1.63). Baseline height and BMI Z scores of around -0.5 on average indicate a degree of growth impairment and nutritional deficiency. Nearly a third of patients (29%) had been diagnosed with either impaired glucose tolerance or CF-related diabetes mellitus (CFRDM), and a large majority were pancreatic insufficient. The mean (SD) baseline vitamin D level

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was 64 (21) nmol/L with 22 (20%) patients insufficient (<50). The ethnicity of the entire sample was Caucasian.

At the time of their initial scan, 9 (8%) patients demonstrated low BMD (height adjusted BMD Z score less than −2 SD (17)), whilst at the most recent scan there were 14 (13%). Four (4%) patients had experienced a fracture prior to their first scan, which increased to 15 (14%) by the time of their final scan during the study period. The recording of fracture was insufficient to determine whether they were traumatic or non-traumatic fractures. Participants demonstrated a mean (SD) 0.06 (0.24) annual decrease in lumbar spine BMD HAZ score.

Associations with BMD

In the univariable regression, for participants with at least two BMD HAZ scores (n=108) the strongest predictor of current BMD HAZ score was found to be previous BMD HAZ score. On average there was a 0.87 SD increase in current BMD for each SD increase in previous BMD (95% CI (0.79, 0.96), p<0.001) (Table 3). Correspondingly, Figure 1 shows a positive linear association between BMD HAZ scores from the first and final DXA scan for each patient who had at least two scans (n=108). The time between each patient's first and final scan ranged from 0.8 to 10 years, with a median duration of 3.6 years (IQR (2.0, 5.1)). Over the duration of the study period, four patients had a BMD HAZ that improved from low (Z <-2) to normal (Z>-2). Two of these participants also had instances where BMD HAZ decreased from normal to low, with all BMD HAZ scores being close to -2 (range -1.7 to -2.1). An additional seven patients had a decrease in BMD HAZ from normal to low. Strong evidence of a positive association was also found with FEV_1 and BMI Z scores, with an increase of approximately 0.25 SD in BMD for each SD increase in these measures (p<0.001 and p=0.004 respectively), and a more modest association with weight Z score (coefficient 0.17, p=0.019). Age (coefficient -0.07, 95% CI (-0.11, -0.02), p=0.005), previous fracture (coefficient -0.72, 95% CI (-1.14, -0.29), p=0.001), use of high dose oral corticosteroids

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(coefficient -0.42, 95% CI (-0.73, -0.10), p=0.01), and an increasing number of hospital admissions in the 12 months preceding the scan (coefficient for 3 or more -0.75, 95% CI (-1.13, -0.38), p<0.001) were associated with lower BMD HAZ scores (Table 3). No evidence of an association with BMD HAZ score was found for any of the remaining measures examined.

After adjusting for previous BMD HAZ score, evidence of a positive association remained only with weight, BMI and FEV_1 Z scores (p=0.038, 0.005 and 0.007 respectively) while the number of hospital admissions (p=0.02) was the only measure to show evidence of a negative association. For all these measures the strength of the association was reduced by adjusting for previous BMD HAZ score. Thiswas the strongest predictor of subsequent BMD HAZ scores.

Discussion

This is a large study of BMD in a population of paediatric patients living with CF and outlines the importance of evidence-based DXA screening guidelines in CF, emphasised by the fact that only 45% of patients had a DXA performed. A reduction in height adjusted BMD at the lumbar spine was associated with previous low BMD HAZ-score, poor lung function, worse nutritional status, age, previous fracture, use of high dose oral corticosteroids, and an increasing number of hospital admissions *per* year. However, after adjusting for previous BMD HAZ score, height adjusted BMD Z score was only associated with FEV_1 Z score, BMI Z score, weight Z score and hospitalisations.

BMD (in gm/cm^2) normally increases 3-5% per year in the pre-pubertal years and 10-15% per year during puberty; smaller gains will cause a resultant fall in Z scores (18). Using the International Society for Clinical Densitometry's definition for low bone mass, 8% of subjects demonstrated a lumbar spine BMD HAZ score lower than -2 at their initial scan after adjustments for age and gender. This was lower than a similar Polish study by Sands et al

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(19), who reported 17% of children and adolescents with CF experienced very low BMD, however they were not height-adjusted and hence may not be as low as reported.

Importance of height adjusted Z score

Several studies have shown that when adjusted for height, the deficit in BMD Z scores in children and adolescents with CF are attenuated, and may on occasion actually result in normal BMD assessment when corrected this way (20, 21). By using height adjusted Z scores, our analyses therefore avoided this potential confounder.

Our study cohort was, on average, just over half an SD shorter at their first scan than a normal gender and age-matched population. This was unsurprising given children with CF often experience pubertal delay and slower growth rates compared to unaffected children.

Associations with low BMD

Several large investigations in unselected CF populations have found lung function to be correlated with BMD (21-24). Our study supports these findings, which found FEV_1 Z score to be strongly associated with BMD under a univariate regression model.

Nutritional status as represented by BMI has also been shown to be strongly associated with bone disease, in line with studies that have investigated the influence of fat mass and body composition on bone density. Bianchi et al. investigated fat mass in young CF patients, finding a strong correlation ($r=0.59$, $p<0.02$) with BMD at the lumbar spine (25). However, Bianchi also suggested that fat mass was a stronger predictor of bone density compared to BMI ($r=0.42$, $p<0.05$). Although this study used a different measure of association to our study, both studies concluded that a measure of nutritional status was positively associated with bone density.

Additionally, patients requiring at least 3 admissions with intravenous antibiotics *per* year demonstrated significantly lower lumbar spine BMD results. These support the recent suggestions that pro-inflammatory cytokines associated with chronic infection may be linked

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to the catabolic state and stimulate osteoclast induced bone resorption and decrease bone formation (26). Patients frequently admitted for IV therapy are also generally more unwell and may experience poorer nutrition and respiratory function than their healthier counterparts. In support of this, the influence of chronic inflammation on BMD was first investigated by Haworth (27), and later supported by Buntain et al., who found an association between both C-reactive protein as a marker of inflammation, and the number of recent hospitalisations, with bone density(24).

Whilst there was an association between previous fracture and high dose corticosteroids with low BMD, this was no longer evident after adjusting for previous BMD HAZ scores.

Other studies have shown a link between increased forearm fracture incidence and a lower bone density in healthy children (28). Likewise, we found a significant difference in BMD HAZ score between participants with and without a positive fracture history. However, this disappeared once we adjusted for previous BMD HAZ score.

Corticosteroids are a well-known risk factor for bone disease and studies have previously shown that children and adolescents with prolonged corticosteroid exposure have higher risk of low BMD (29). Whilst our study found an association with oral corticosteroid use and low HAZ BMD in the unadjusted analysis, there was no association between corticosteroid use and BMD once adjusted for previous BMD. This may reflect the underreporting of corticosteroid use in medical records, the different thresholds for positive corticosteroid exposure in our cohort or the generally lower prescribing of corticosteroids in modern therapeutic regimes for CF. Nevertheless, the well-established role of corticosteroids in poorer bone health means the use of corticosteroid therapy should still be monitored closely.

Our data did not support an association between BMD and CF genotype, CF-related diabetes mellitus, chronic infection with *Pseudomonas aeruginosa* or vitamin D level.

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Longitudinal Component

Several recent studies have suggested that bone disease and reduced rates of bone accrual affect CF children more so than adolescents. Gronowitz et al. found adolescents aged between 13 and 16 demonstrated a similar increase in BMD at the lumbar spine compared to Swedish reference data (30). Similarly, before adjusting for height, Buntain found reduced gains in BMD in Australian children over a 2-year period, while adolescents increased areal BMD at an equivalent rate when compared to healthy controls (20). However, after adjusting for short stature, adolescents also demonstrated reduced bone mineral accrual. Kelly et al (31) reported normal bone mass accrual in a cohort of children and adolescents with CF and comment on the inconsistency of reports of low BMD in youth with CF. Our study, which investigated predominately adolescents, supports these findings as participants demonstrated very minimal annual decrease in lumbar spine BMD Z score, mean (SD) -0.06 (0.24).

Limitations

As with all retrospective investigations, the major limitation of this study involved information bias and inaccurate recall of participant exposure to risk variables. This particularly applied to gathering data from case records, discharge summaries and radiology reports regarding use of inhaled and oral corticosteroid, and evidence of previous fractures. The treating clinician may not have recorded these risk factors, or patients may have sought treatment for these medical issues outside the CF centre and hence were not included in the study. There are also discrepancies in the time points of lung function and biochemical data collection. As the dates of these investigations may not match the date of the DXA scan, results closest to the DXA scan date within a 3 month period were used. If there was no lung function data available within this time period relative to the DXA scan, it was not included. This accounts for the missing FEV_1 Z scores for some patients.

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Less than half of the original patient cohort had a DXA scan over the study period, possibly reflecting the overall approach to BMD screening. However, there was likely a bias towards patients with more clinical concerns who were selected for DXA scans. This is supported by the relatively low FEV_1 Z score and high rate of CFRD in the study cohort.

The ISCD recommendations in 2013 (32) include total body less head as a recommended DXA imaging site for paediatric patients. Most of this data predates that, so only lumbar spine was used for analysis.

Another major limitation was the inability to measure key characteristics at the time of the DXA scans, including puberty and physical activity levels. Studies have shown a positive correlation between bone density and puberty(25) and physical function(24, 33). Children with CF often experience delayed onset of puberty and reduced levels of physical activity, which may contribute to lower bone mineral density.

Fracture data are crucial to analysis as a main marker of bone health, but there was no association between fractures and BMD found in our cohort, once adjusted for previous BMD. This may reflect the underreporting of fractures, given the method of ascertainment via radiology and case notes in our study, or that the fracture rate in our cohort is no greater than the non-CF population(34). Compared to data in adults, where increased fracture prevalence has been reported(4), children and adolescents may be more vulnerable to complications of poor bone health in the future despite no clinical signs at this age.

Future directions

Based on our findings, it is clear that prior BMD is the biggest driver of future BMD. Therefore, screening protocols driven by the baseline result can rationalise the number of scans that the patient needs to undertake. We suggest a new pragmatic guideline for monitoring of bone health in CF patients where results of the initial DXA guides the follow-up interval, similar to the US and European Society guidelines(10, 11). Additionally, patient

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factors of FEV_1 Z score, BMI Z score and frequent hospitalisation are included to reflect the known impact on BMD. The proposed guideline, (Figure 2) recommends a baseline DXA at the age of 8 for all patients with CF. For those with a HAZ score of -1 SD or better, we recommend a repeat DXA in 5 years (Stream 1). For those with a HAZ score between -1 and -2 SD, they should have a repeat DXA in 2 years (Stream 2). For those patients with evidence of significant bone health impairment with a HAZ score worse than -2 SD, they should proceed to yearly scans (Stream 3). If the patient develops one of the following, they are moved up a stream to the next level of monitoring: FEV_1 Z score below -2, BMI Z score below -2 or frequent hospitalisation (characterised by 3 or more admissions per year). The FEV_1 and BMI Z score cut-offs correspond with measurements below the 2.5^{th} percentile as a clinical correlator of disease significance. Studies of interventions based on such screening and monitoring frameworks for BMD in CF are needed.

Conclusion

In a large unselected cohort of Australia paediatric cystic fibrosis patients, poor bone health remains a problem. The main predictor of future bone mineral density was previous bone mineral density. However, once previous BMD was accounted for, FEV_1, BMI and weight Z scores plus the number of hospitalisations remained markers of disease severity, and may be useful markers of future BMD, particularly in those patients who experience a change in clinical status. Other factors initially believed to be useful markers of decreasing BMD, including previous fracture and use of high dose oral corticosteroids, no longer showed an association after this adjustment. This information is useful in the implementation of future screening guidelines, as patients with a good DXA score at baseline who remain stable without clinical deterioration, may not require second yearly scans, as their BMD also tends to remain stable. If their clinical progression changes, then DXA monitoring needs to be reviewed. For a cohort that is already heavily burdened by the significant morbidity of this

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chronic condition, the unnecessary screening in patients with a perceived low risk of bone disease would be greatly beneficial.

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***Table 1**: Number of DXA scans per patient*

Number of scans per patient	**Frequency**	**Percentage**
1	83	43
2	59	31
3	22	12
4	18	9.4
5	4	2.1
6	4	2.1
7	1	0.5
Total	191	100

Table 2 Demographic and available clinical characteristics of study participants at the time of their initial DXA scan (n=108)

	Number nonmissing	**Mean (SD) or Number (%)**
Age (years)	108	12.6 (2.2)
Gender	108	
Male		54 (50%)
Female		54 (50%)
Genotype	104	
Phe508del homozygous		57 (55%)
Compound heterozygous		38 (37%)
Other		9 (9%)
Height Z score	108	-0.53 (1.27)
BMI Z score	104	-0.49 (0.99)
FEV_1 Z score	75	-2.12 (1.63)
Vitamin D level (nmol/L)	88	64 (21)
Glucose tolerance	95	
Normal		67 (71%)
Impaired		12 (13%)
CFRDM		16 (17%)
Pancreatic status	108	
Sufficient		15 (14%)
Insufficient		93 (86%)
Fracture history	108	
No fractures		104 (96%)
Fractures		4 (4%)
Corticosteriod use	102	
None		71 (70%)
Inhaled only		19 (19%)
Oral only		5 (5%)
Both		7 (7%)
LSBMDZ	108	

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LSBMDZ ≥-2		99 (92%)
LSBMDZ <-2		9 (8%)

BMI=body mass index, FEV_1=forced expiratory volume (litres) in 1 second, CFRDM=cystic fibrosis related diabetes mellitus, LSBMDZ=lumbar spine bone mineral density Z score

Linear regression on BMD HAZ score allowing for clustering *(n=108 participants)*

	Univariable regression					Adjusted for previous BMD HAZ score			
	n	**Coefficient**	**95% CI**	**p-value**	**R-squared**	**n**	**Coefficient**	**95% CI**	**p-value**
Previous BMD HAZ score	199	0.87	(0.79, 0.96)	**<0.001**	74.0				
Height Z score	307	0.03	(-0.10, 0.16)	0.652	0.2	199	0.03	(-0.03, 0.09)	0.364
Weight Z score	292	0.17	(0.03, 0.32)	**0.019**	4.3	188	0.08	(0.004, 0.15)	**0.038**
BMI Z score	292	0.26	(0.08, 0.44)	**0.004**	7.2	188	0.12	(0.03, 0.20)	**0.005**
FEV1 Z score	238	0.23	(0.14, 0.33)	**<0.001**	17.0	163	0.07	(0.02, 0.12)	**0.007**
Age at Scan (yrs)	307	-0.07	(-0.11,-0.02)	**0.005**	3.2	199	-0.02	(-0.05, 0.01)	0.266
Vitamin D level	253	0.002	(-0.004, 0.01)	0.464	0.4	165	-0.001	(-0.004,0.002)	0.541
Gender Reference group: Male	307				0.0	199			
Female		0.02	(-0.34, 0.39)	0.894			0.06	(-0.07, 0.19)	0.378
Genotype Reference group: Phe508del homozygous	299			0.837	0.4	195			0.242
Compound heterozygous		-0.02	(-0.42, 0.37)				-0.10	(-0.25, 0.04)	
Other		0.17	(-0.48, 0.83)				0.05	(-0.16, 0.25)	
Pancreatic status	3				1.2	1			

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	07					99			
Reference group: Sufficient									
Insufficient		0.30	(-0.33, 0.92)	0.348			0.12	(-0.11, 0.35)	0.311
	285			0.425	0.9	190			0.740
Glucose tolerance									
Reference group: Normal									
Impaired		-0.03	(-0.46, 0.40)				-0.05	(-0.24, 0.14)	
CFRDM		-0.21	(-0.53, 0.12)				-0.06	(-0.22, 0.10)	
	307				5.4	199			
Fracture history									
Reference group: No fractures									
Fractures		-0.72	(-1.14,-0.29)	**0.001**			-0.16	(-0.34, 0.02)	0.085
	288				1.2	186			
Pseudomonas colonisation									
Reference group: Not Colonised									
Colonised		-0.21	(-0.55, 0.12)	0.207			0.04	(-0.11, 0.19)	0.601
	295				0.4	191			
Inhaled Corticosteroid									
Reference group: No									
Yes		0.14	(-0.28, 0.56)	0.509			-0.13	(-0.30, 0.03)	0.108
	290				1.9	188			
Oral Corticosteroid									
Reference group: <1 month/low dose									
≥1 month/high dose		-0.42	(-0.73,-0.10)	**0.010**			-0.10	(-0.31, 0.10)	0.324
	307			**<0.001**	10.3	199			**0.020**
Number of admissions									
Reference group: 0									
1 or 2		-0.34	(-0.67,-0.01)				-0.15	(-0.31, 0.02)	
3 or more		-0.75	(-1.13,-0.38)				-0.22	(-0.38,-0.07)	

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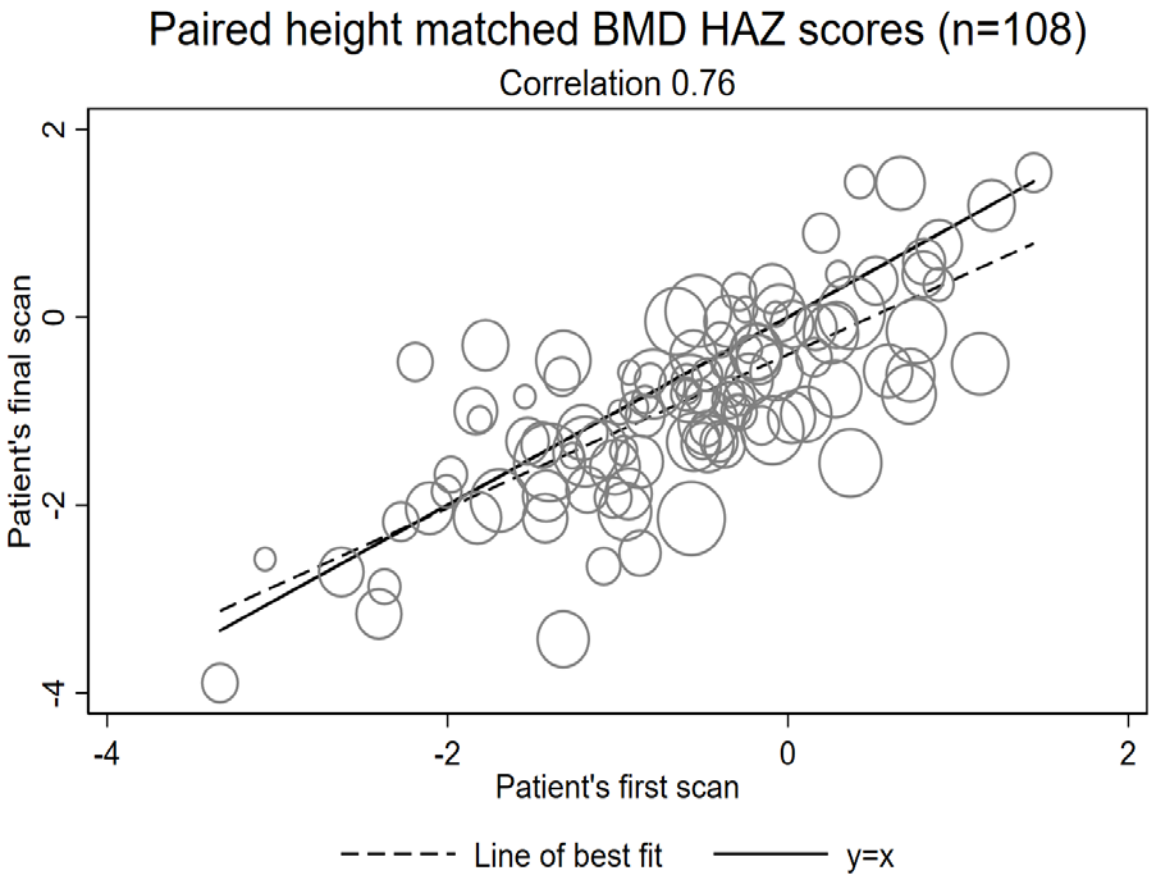

Figure 1 First DXA versus final DXA for patients with two or more BMD HAZ scores Legend: The dot plot shows the number of years from each patient's first to last scan. The size of the bubble is proportional to the number of years between these scans.

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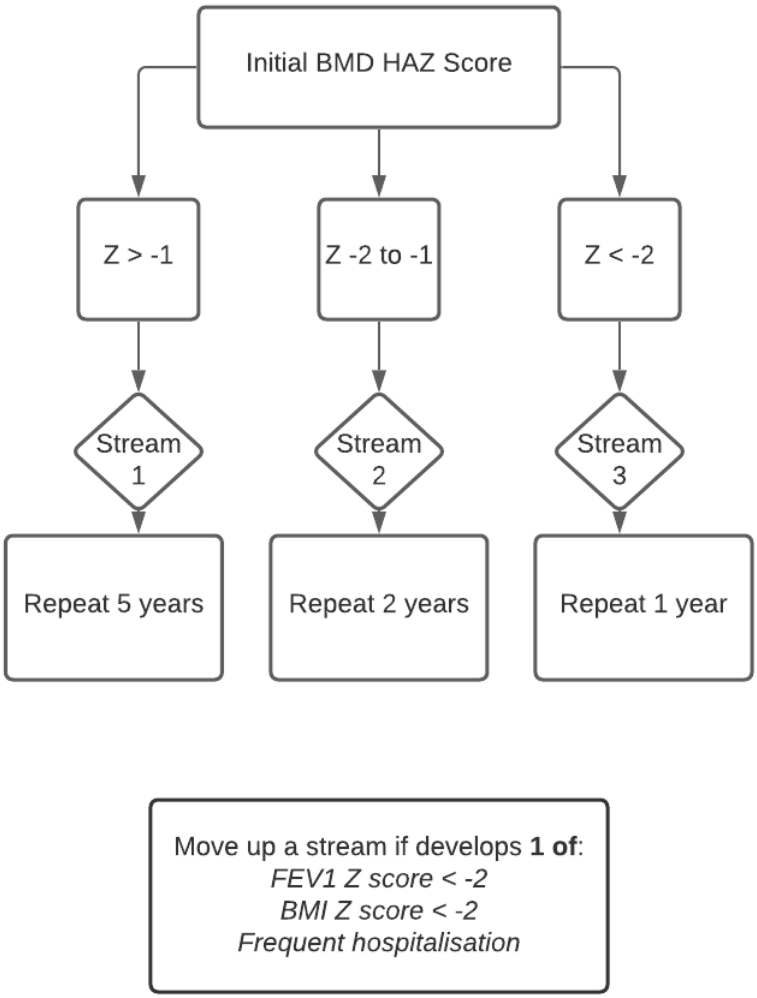

Figure 2 Proposed algorithm for BMD monitoring in patients with CF Legend: Frequent hospitalisation refers to 3 or more admissions per year.

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