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Original Article

Cystic fibrosis-related bone disease explored using a four step algorithm

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Abstract

Background: A suboptimal bone accrual in young individuals with cystic fibrosis (CF) may be related to the development of a premature CF-related bone disease. Dual energy X-ray absorptiometry (DXA) is the mainstream measure of bone health; however, the influence of body size and lean tissue mass (LTM) on bone data is poorly interpreted.
Methods: Total body dual-energy X-ray absorptiometry (DXA) measurements of bone mineral content (BMC) and LTM in 53 individuals with CF (7.00–17.99 years) were compared to 53 sex-matched controls. BMC, height, and LTM in relation to height and BMC Z-scores were calculated and used in a 4-step algorithm.
Results: Pubertal females with CF had less total body BMC for age ($p = 0.02$); pre-pubertal males ($p = 0.05$) and pubertal females with CF ($p = 0.03$) were shorter; and pubertal females with CF showed less total body BMC for LTM ($p = 0.01$).
Conclusions: The algorithm showed the following: (1) prior to puberty lowered total body BMC was primarily due to short stature, (2) LTM was appropriate for body size, and (3) pubertal females with CF had significantly less total body BMC for their LTM. Longer controlled trials are needed to clinically interpret CF-related bone disease using DXA derived data that considers patient size and body composition.

Keywords: Cystic fibrosis; BMC; Height; LTM; DXA; Algorithm

1. Introduction

Adults with CF have an increased risk of fracture [1,2]. This increased risk may be linked to an inadequate bone mineral accrual during the childhood years, and be independently associated with a reduced amount of lean tissue mass (LTM) [3].

Dual-energy X-ray absorptiometry (DXA) has been a useful modality to gain an increased understanding of bone health in individuals with CF [3–10]. Clinical evaluations are based on areal bone mineral density (aBMD) as a function of bone mineral content (BMC) in the projected bone area, measured in g/cm^2 (aBMD = BMC/bone area, g/cm^2), and compared to age- and sex-matched reference data. Short stature is common in individuals with CF [3,5]. The small body size will result in reduced total body aBMD and BMC, which can be misinterpreted as an abnormally low result when compared to typically developing age and sex specific reference data [11–14]. The International Society of Clinical Densitometry (ISCD) 2013 position statement, therefore, recommends to adjust for stature in the interpretation of paediatric bone health [15], but this is yet to be implemented in many clinical settings.

When adjusted for body size, aBMD and BMC results are similar in individuals with CF compared to controls [5,6,8,9].

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Longitudinal work in individuals with CF demonstrates LTM to be an independent predictor of height adjusted aBMD [3]. Moreover, aBMD results that have been adjusted for height and LTM, to explain resultant bone deficits as a functional muscle–bone relationship, reveal no significant differences in total body and regional aBMD in individuals with CF compared to matched controls [5].

Applying the 4-step algorithm of Högler et al. [12], which considers height and LTM when interpreting DXA data, may account for individual differences in body size and LTM, and allow for the examination of muscle and bone relationships. Our study aimed to assess if low aBMD, measured by DXA, was due to: an intrinsic bone problem, by way of reduced BMC; reduced LTM; or a combination of both, in young individuals with CF. This allowed the following important questions to be clinically addressed: (1) does BMC develop appropriately for the associated LTM; and (2) is there a need to place emphasis on increasing BMC by increasing LTM?

2. Methods

2.1. Subjects

Individuals with CF, aged between 7.00 and 17.99 years who attended the Royal Children's Hospital (RCH), Brisbane, Australia, were invited to participate in this cross-sectional study of bone health in CF. The diagnosis of CF had been confirmed by an elevated sweat chloride test. Individuals with CF were excluded if they had a primary bone disorder, or were awaiting lung transplantation. A comparison was made to healthy controls, of the same age, recruited from local primary and secondary schools in the Brisbane region. Exclusion criteria for the control group included: chronic medical conditions known to affect growth, nutritional status or bone health; use of oral corticosteroids ≥ 2 weeks; and/or immobilisation ≥ 1 week, in the preceding 12 months of the recruitment period. Only controls of European-Australian ancestry were included so as to be comparable to the CF cohort.

Approval for the study was obtained from the Medical Research Ethics Committee, The University of Queensland and the Royal Children's Hospital and Health Service District Ethics Committee. Informed consent to participate was obtained by all participants prior to testing. Assent by oral agreement was given by participants under 10 years of age, and written informed consent was provided by all legal guardians and participants over the age of 10 years.

2.2. Clinical assessment

Height was measured (Magnimeter, Raven Equipment, UK) to be 1 mm and weight was determined to be 0.05 kg (Tanita BWB-600 Wedderburn Scales, Australia). BMI (kg/m^2) was calculated as weight/height^2. Standard deviation Z-scores for height, weight and BMI for each subject were calculated relative to the Centers for Disease Control and Prevention (CDC) 2000 growth data [16]. Spirometry testing was performed only in the CF cohort at the RCH respiratory laboratory. The best FVC and FEV_1 were recorded and expressed as percentage predicted [17]. Left hand-wrist X-rays were obtained for the determination of bone ages, calculated by one reader (DB) using the Tanner–Whitehouse (TW3) method [18]. Self-assessed pubertal status was attained via pictorial illustrations [19], where puberty was defined as Tanner stage ≥ 2. Vitamin D levels were measured [20]. A vitamin D level < 50 nmol/L [21] was used to determine vitamin D insufficiency.

The following data were collected via retrospective hospital chart reviews or history recall: genotype; pancreatic sufficiency status; oral and/or inhaled corticosteroid use for the 6 months prior to the project; and the presence of pseudomonas aerial infection. Incidence of any fractures in the 6 months prior to testing date was questioned directly for all subjects.

2.3. Densitometry

Using standard procedures, a total body (including head) DXA scan (Prodigy, GE Medical Systems, LUNAR, Madison, WI, USA) was used to obtain total body BMC (g) and LTM (g) for all study participants. Scans of the anterior posterior (AP) spines L1–L4 were additionally acquired. All results were reported as mean ± SD. The departmental operator precisions for the measured sites were 1% for the total body scans across the study. Daily calibration of the DXA was performed on the morning prior to each measurement using an aluminium spine phantom. All images were acquired and analysed by the principal investigator (DB) using the manufacturer's paediatric software (enCORE, version 11.4).

2.4. 4-step algorithm

This algorithm provides a classification to better describe CF-related bone disease when using total body DXA data, according to a possible biomechanical pathogenesis [22]. The algorithm is total body specific as it supplements the problematic total body age aBMD Z-score in abnormally sized individuals. Initially, height is considered, then any low aBMD may be the result of low bone accrual (BMC), low LTM or a combination of both BMC and LTM. To determine if a low BMC was body size related, total body BMC Z-scores (Australian paediatric reference database [12]) and height Z-scores [16] were used with the 4-step algorithm [12]. Log–log regression was used to normalise LTM for height and total body BMC for LTM using the same Australian paediatric database. The value for each Z-score was assigned as: low (<-1); normal (≥ -1 to 1); or high (>1). For example, when following steps 1 to 4 in Fig. 1, a low BMC for age, when accounted for height, may result from poor bone accrual, low LTM, or a combination of both scenarios BMC and LTM, respectively.

The AP spine data was not used in the algorithm as the: (1) generation of spine BMC is based on an estimate of fat mass of the adjacent soft tissue. The inhomogeneity of fat distribution in the soft tissue overlying and adjacent to the AP spine causes large variations in BMC [23,24]; (2) biomechanical relationships of BMC to LTM are specific to the striated skeletal muscle and bone physiology, largely at the periosteal bone