ELSEVIER
Journal of Cystic Fibrosis xx (2016) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Multiple prevalent fractures in relation to macroscopic bone architecture in patients with cystic fibrosis☆,☆☆

Mirjam Stahl [a,*], Christian Holfelder [b], Carolin Kneppo [c], Meinhard Kieser [d], Christian Kasperk [e], Eckhard Schoenau [f], Olaf Sommerburg [a,1], Burkhard Tönshoff [c,1]

[a] Division of Pediatric Pulmonology, University Children's Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany
[b] Department of Pediatric Radiology, University Children's Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany
[c] Department of Pediatrics I, University Children's Hospital Heidelberg, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany
[d] Institute of Medical Biometry and Informatics, University Heidelberg, Im Neuenheimer Feld 153, 69120 Heidelberg, Germany
[e] Department of Medicine I, University Hospital Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany
[f] Children's Hospital, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany

Received 2 March 2016; revised 31 May 2016; accepted 6 June 2016

Abstract

Background: The relative risk for bone fractures in patients with cystic fibrosis (CF) and its relationship to macroscopic bone architecture assessed by pQCT and DXA are incompletely defined.
Methods: In a cross-sectional study of 43 CF patients (age, 17.8 ± 6.2 years), rate and location of fractures, bone mass, density, geometry, and strength of the radius as well as forearm muscle size were investigated.
Results: The fracture rate in CF was 9.2-fold higher compared to an age-matched German control population. The probability of remaining free of any fracture in CF patients at 25 years was reduced to 39.8% compared to 84.6% in controls ($P < 0.001$). Assessment of macroscopic bone architecture by DXA and pQCT allowed the differentiation of patients with multiple prevalent fractures with a high sensitivity (up to 100%) and specificity (up to 94.3%).
Conclusions: Bone densitometry is a useful tool for noninvasive assessment of fracture risk in CF patients.

Keywords: Cystic fibrosis; Bone disease; Fracture rate; Macroscopic bone architecture; Bone densitometry; Noninvasive monitoring

1. Introduction

With increasing life expectancy, secondary diseases such as cystic fibrosis (CF)-related bone disease emerge, which contribute significantly to patients' morbidity. CF-related bone disease is the second most common non-pulmonary complication after CF-related diabetes in these patients. First described in 1979 [1], its incidence and prevalence have increased since the 1990s both in adults and adolescents with CF [2,3]. Nowadays, bone disease is apparent in almost every fourth adult CF patient [4]. The risk factors for the development of osteopathy in CF and its pathogenesis remain incompletely characterized [5]. Recent evidence suggests that it is rather an

☆ Author's contributions: Conception and design: MS, OS, BT. Acquisition, analysis and interpretation of data: MS, CH, CKn, MK, CKa, ES, OS, BT. Writing the manuscript or revising it critically for important intellectual content: MS, OS, BT.

☆☆ This study was supported by grants from the Dietmar Hopp Foundation and the Mukoviszidose e.V. (A03/06). The sponsors of the study had no role in study design, data collection, data analysis, or writing of the report.

* Corresponding author at: University Children's Hospital, Im Neuenheimer Feld 430, 69120 Heidelberg, Germany. Tel.: +49 62215637049; fax: +49 6221565281.
E-mail address: mirjam.stahl@med.uni-heidelberg.de (M. Stahl).

[1] Both authors contributed equally to this study.

http://dx.doi.org/10.1016/j.jcf.2016.06.004
1569-1993/

inadequate accretion of bone mineral than bone loss, which plays a major role [6].

The clinical consequence of bone disease is bone fragility. Several studies reported an elevated fracture rate in adult CF patients [3,4,7–9], but a precise risk assessment for the development of fractures compared to a reference population has not been carried out. These fractures occur both at sites of high cancellous bone, such as the vertebrae, and at sites of mainly cortical bone, such as the peripheral skeleton [5]. There is strong evidence that fractures result from low bone density (BMD), because BMD accounts for 75–85% of the variance in the ultimate strength of bone tissue [10] and the risk of fracture increases two- to threefold for each standard deviation fall in the BMD below the mean for a healthy population of the same age [11]. Several previous studies have investigated bone mass in patients with CF and have described decreased BMD and bone mineral content (BMC) in 11 to 57% of patients. However, the relationship of parameters derived from dual-energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) measurements with bone fragility in CF patients remains unknown. Such a relationship would be important, because it would support the role of bone densitometry for non-invasive monitoring of bone quality in CF patients. We therefore analyzed the relative risk for bone fractures in young CF patients and its relationship with parameters of macroscopic bone architecture derived from pQCT and DXA measurements. Some of the results of these studies have been previously reported in the form of an abstract [12].

2. Methods

2.1. Study design and patients

We performed a cross-sectional study in 43 Caucasian patients (22 males) with CF. Besides a confirmed diagnosis of CF by a sweat chloride concentration > 60 mmol/mL or by CF genetic mutation analysis [13], informed written consent from the patients or parents / legal guardians of all subjects and age 6–30 years were inclusion criteria. Exclusion criteria were (i) a concomitant disease or mental retardation that prevented a regular measurement by pQCT without movement artefacts, and (ii) disorders others than CF known to affect bone and mineral metabolism such as advanced chronic kidney disease, defined as an estimated glomerular filtration rate according to Schwartz [14] < 30 mL/min per 1.73 m², primary hyperparathyroidism, multiple myeloma, thyrotoxicosis, hypothyroidism, or status post lung transplantation. Fracture history of radiographically confirmed fractures since birth was collected *via* a questionnaire (completed by the patients with help of their parents, if applicable) with evaluation of the location (axial *vs.* peripheral skeleton) and mode of acquiring the fracture (high-trauma vs. low-trauma fracture; low-trauma fracture was defined as a fracture occurring spontaneously or from a fall no greater than standing height). Only radiographically confirmed fractures with an available report were used for analysis. None of the patients had additional behavioral risk factors for fractures such as excessive skiing.

Data on chronic pulmonary colonization with *Pseudomonas aeruginosa*, duration of oral and inhaled corticosteroids, supplementation of pancreatic enzymes, vitamin D and calcium as well as insulin therapy were collected by a validated questionnaire [15]. No patient suffered from bone pain at time of investigation. All biochemical and anthropometric data were obtained on the day of pQCT or DXA measurements or within a time frame of one month before or after. Details of measurements of hormonal and biochemical parameters of calcium-phosphate as well as bone metabolism are described in the online data supplement (OLS; Tables E1–E3). Anthropometry and assessment of macroscopic bone architecture are also described in the OLS. For patients up to 19 years of age, bone age (BA) was determined by the method of Greulich and Pyle using radiographs of the left hand [16]. Two sites of the nondominant radius were analyzed by pQCT (XCT-2000 scanner, Stratec Inc., Pforzheim, Germany), the distal metaphysis (4% site) and the proximal diaphysis (65% site), and BMD of the lumbar spine (L1–4) and the total body (head included in adults (TB), head excluded in children (TBLH)), expressed as gram/centimeter^2, and BMC, expressed as gram, were determined by DXA (Hologic Discovery A; Hologic, Boston, MA). More details are available in the OLS.

The study was conducted in full accordance with the principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice guidelines, and approved by the Ethics Committee of the University of Heidelberg (study number 070/2006). Written informed consent of patients and patients' parents or guardians was obtained prior to initiation of any study-related procedure.

2.2. Control populations

The German Federal Statistical Office publishes data on all acquired fractures per year in Germany (www.destatis.de). The population 0–30 years of age in the year 2007 was used as control population for the calculation of fracture rates in this study and comprised 26,370,006 individuals. Because the fracture rate remained stable in this age group during the last ten years, we estimated the number of normal population remaining free of fractures (Kaplan–Meier method) during a similar follow-up period as the CF cohort as described previously [17]. The pQCT and dynamometer results were compared to those of a German reference population from the DONALD study using identical methodology [18–21]. DXA results of CF patients were compared to data from a Caucasian reference population investigated by the manufacturer of the DXA scanner [22]. Results in CF patients were converted into age- and gender-specific *z*-score values using the formula: *z*-score = [(test result for a patient) − (age-specific mean in reference population)] / (age-specific SD in reference population).

2.3. Statistical analysis

Results are expressed as means ± SD, if not indicated otherwise. Normal distribution of data was assessed by the Shapiro–Wilks test. To evaluate whether a parameter was significantly different from control, the difference of the mean

Please cite this article as: Stahl M, et al, Multiple prevalent fractures in relation to macroscopic bone architecture in patients with cystic fibrosis, J Cyst Fibros (2016), http://dx.doi.org/10.1016/j.jcf.2016.06.004